

Highlights from Gnomes Meeting
Birmingham, U.K.
May 20th – 23rd 2015

Stefan Hübscher,

Institute of Immunology and Immunotherapy, University of Birmingham
Departmentt of Cellular Pathology, Queen Elizabeth Hospital, Birmingham

UNIVERSITY OF
BIRMINGHAM



Welcome to the Gnomes in Birmingham 2015 !
The Gnomes go “back to basics”

University Hospitals
Birmingham
NHS Foundation Trust



University of Birmingham – Conference Park

Hornton Grange



Winterbourne House & Gardens





Annual Meetings of the International Liver Study Group

- First meeting, July 1968, University of Zürich (Martin Schmid)
- Currently 15 circulating members (8 Europe, 5 North America, 2 Australia)
- Cases circulated prior to meeting (2-3/ person) to cover particular theme
 - **2015 – “acute hepatitis & acute liver failure”**
- Suggested diagnoses submitted prior to meeting and collated by local organiser
- Cases presented and discussed further at meeting (2 days)
- Aim to reach consensus and provide summary/guidelines
 - Usually a 2 year cycle – 2nd year focuses on specific areas of interest

Causes of Acute Hepatitis / Acute Liver Injury

1. Viral Hepatitis
2. Drugs
3. Autoimmune (alloimmune) hepatitis
4. Other

Causes of Acute Hepatitis / Acute Liver Injury

1. Viral Hepatitis

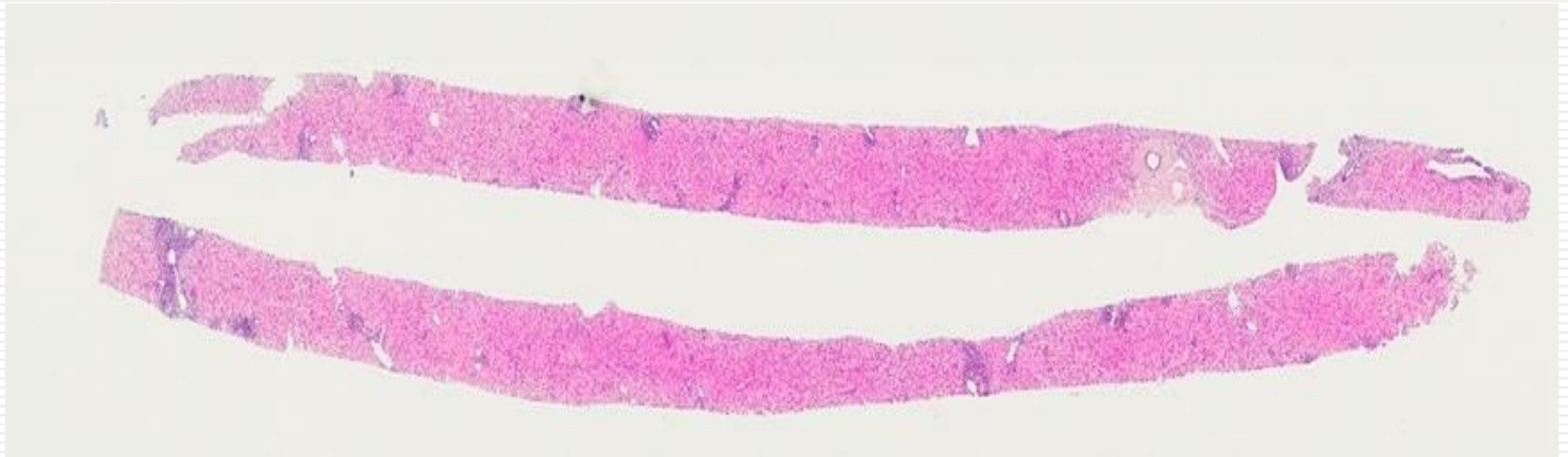
2. Drugs

3. Autoimmune (alloimmune) hepatitis

4. Other

Clinical history

- A 27-year-old woman was admitted to our hospital with a 10-days history of right upper quadrant abdominal pain, progressive tiredness and jaundice.
- Her past medical history revealed a mild hypothyreosis and iv-drug abuse.
- Laboratory test results were the following: ASAT 1278 U/l, ALAT 2477 U/l, gGT 67 U/l, Alk.phos. 175 U/l, bilirubin 87 mmol/l.
- A liver biospy was performed.



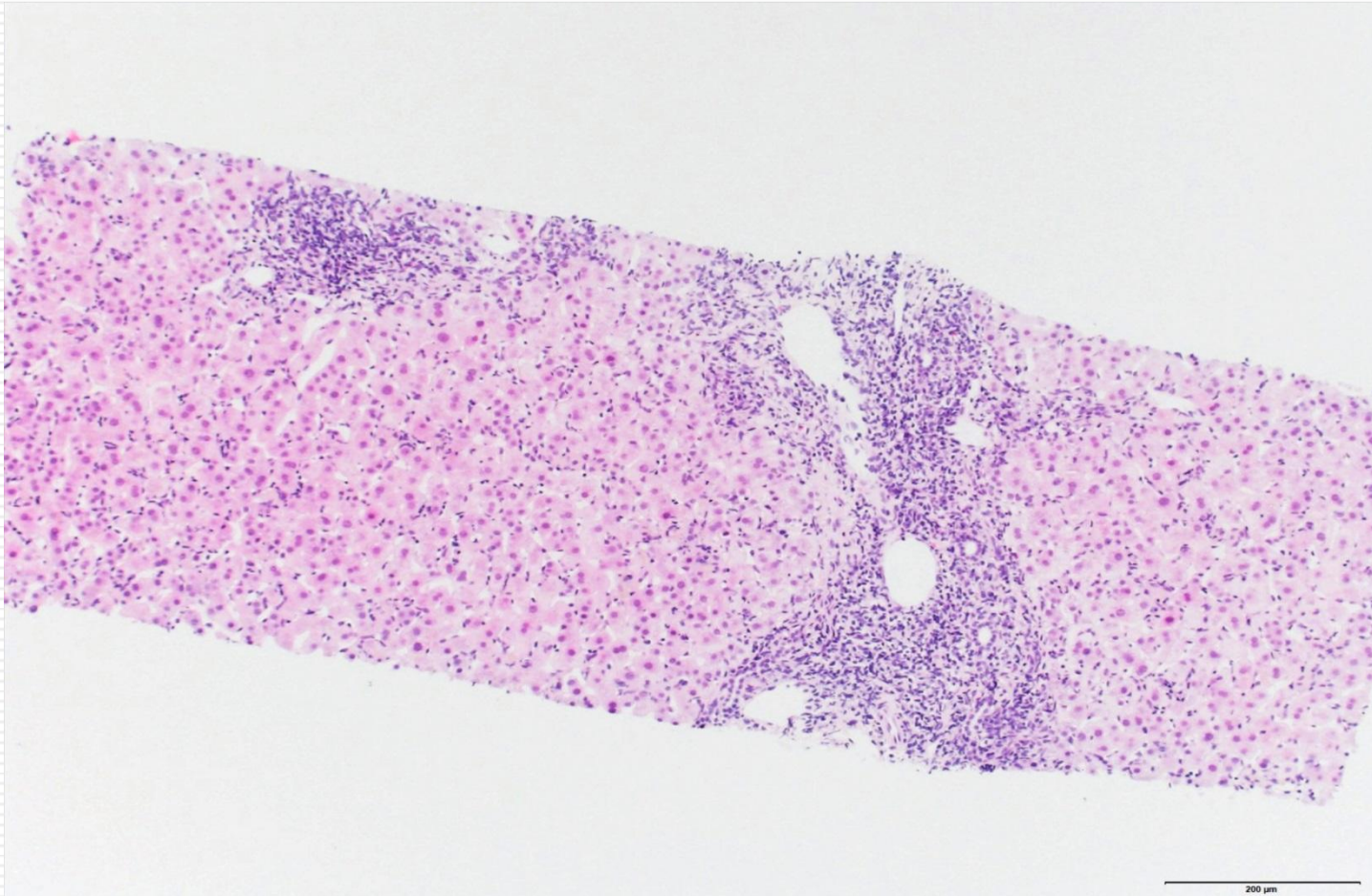
Preserved lobular architecture



No increase of fibrosis

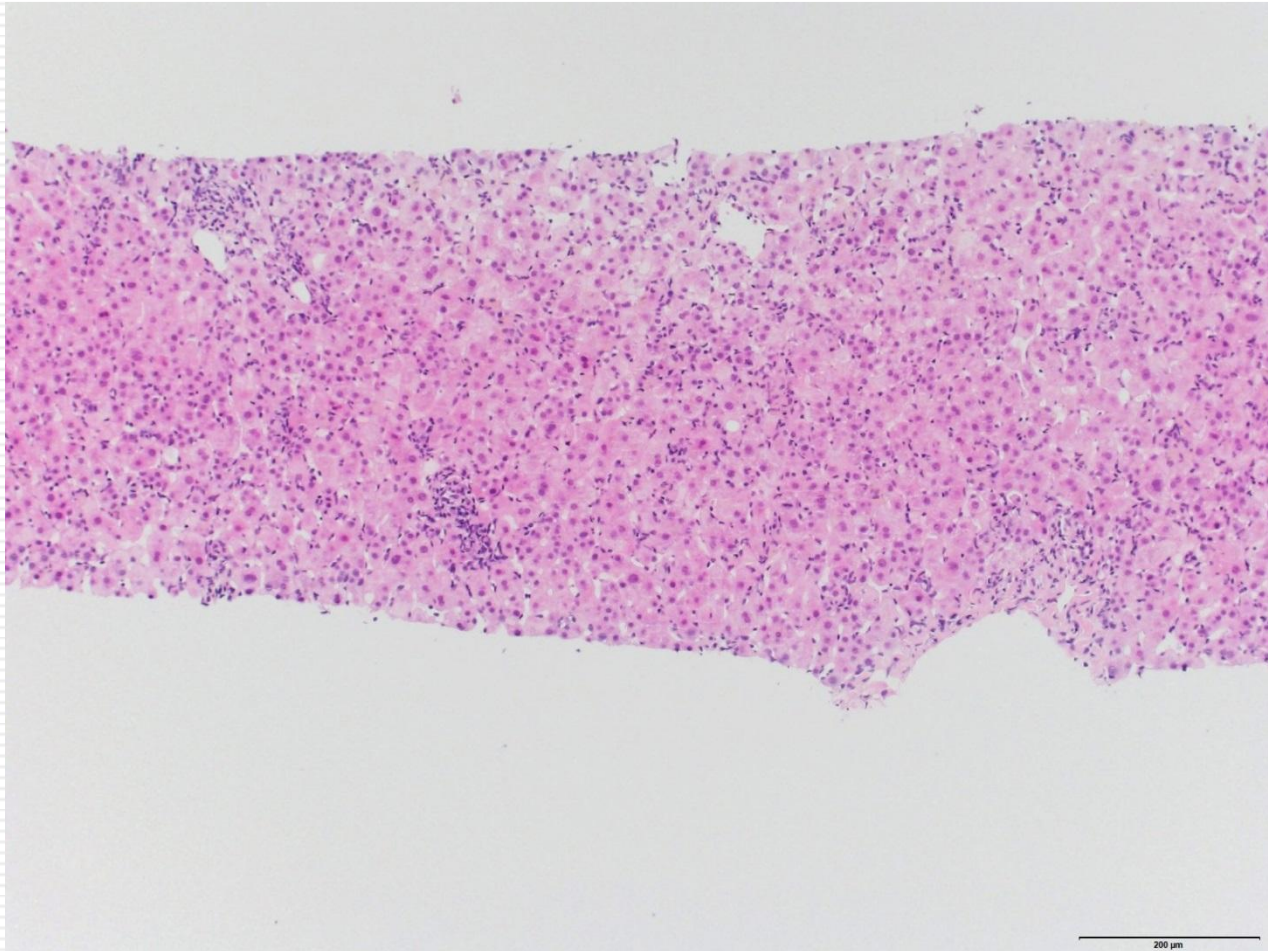
B14.1835

3



Moderate to severe mononuclear inflammatory infiltrates in some PT

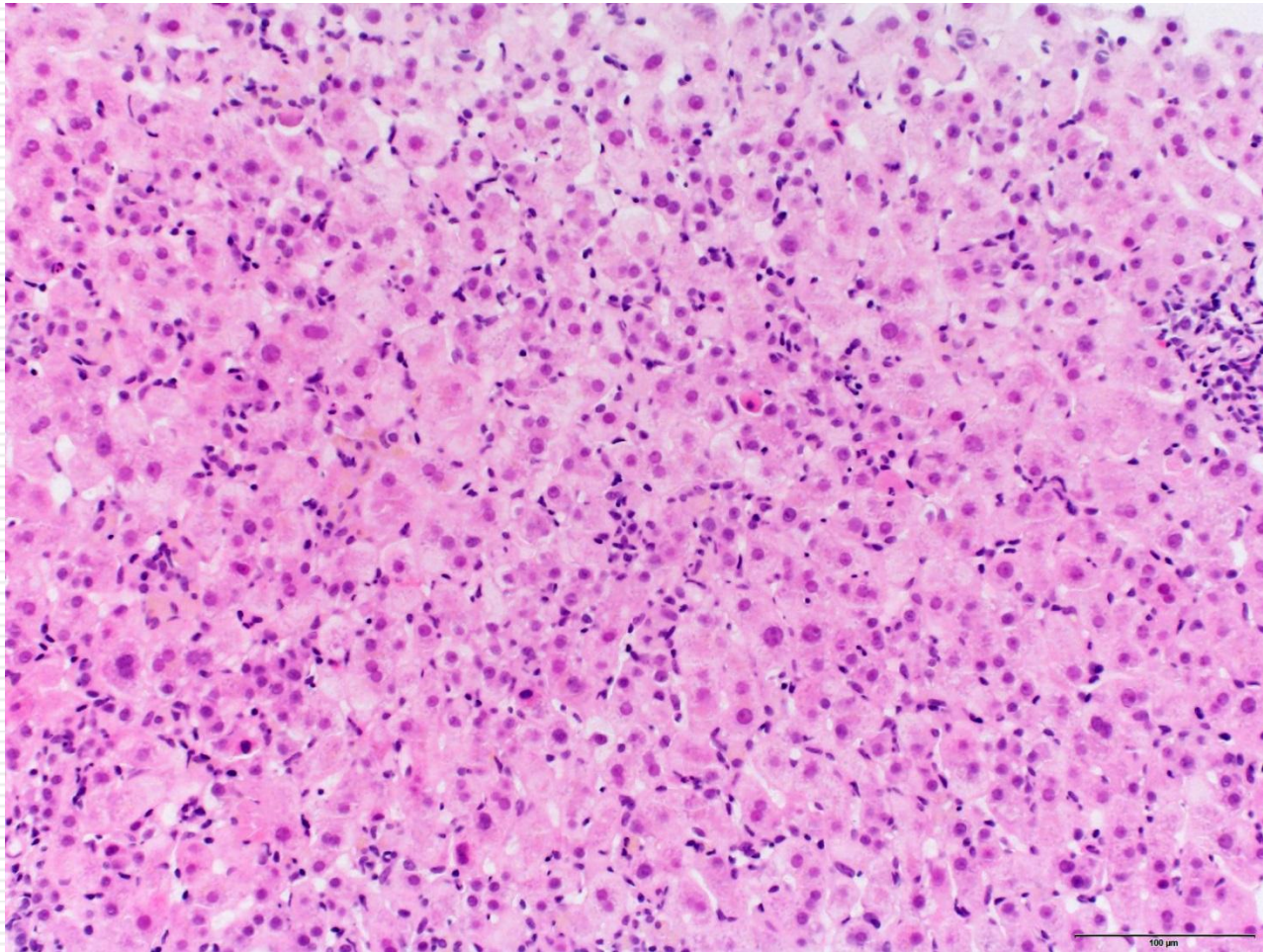
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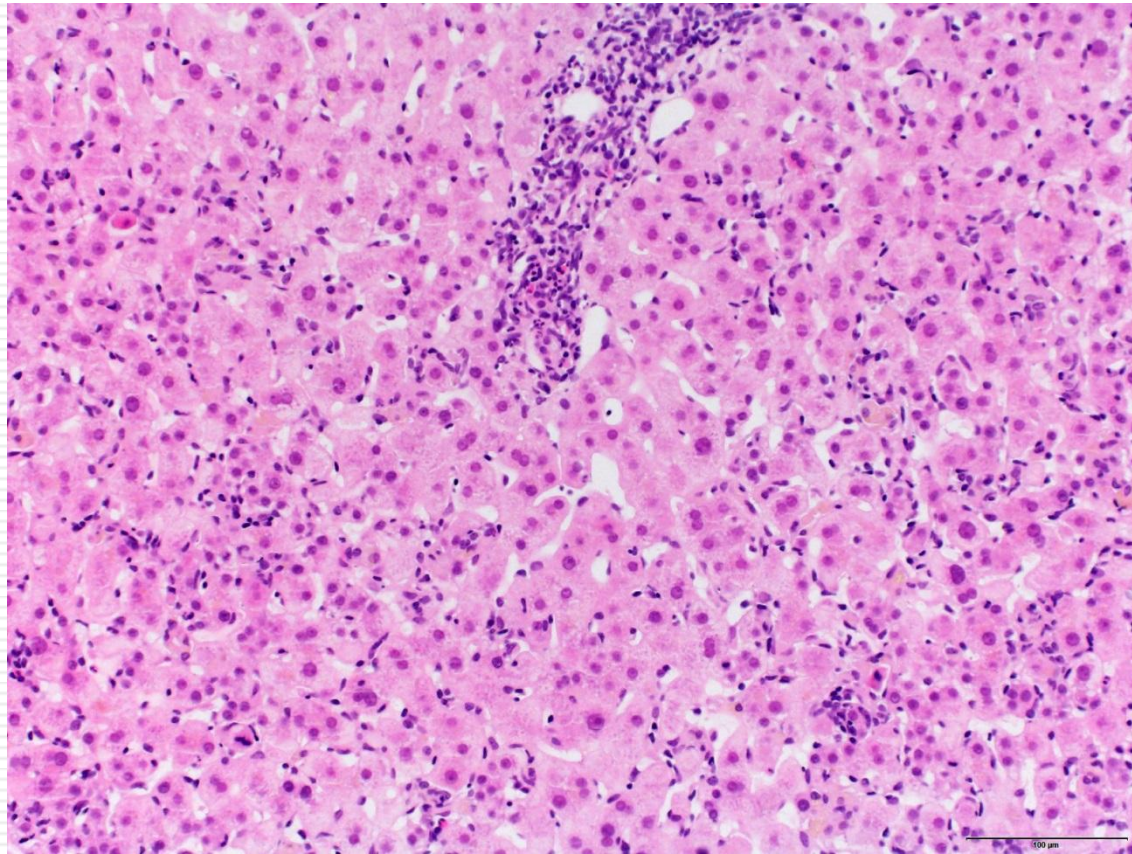
Predominance of lobular lesions: diffuse necroinflammation

B14.1835

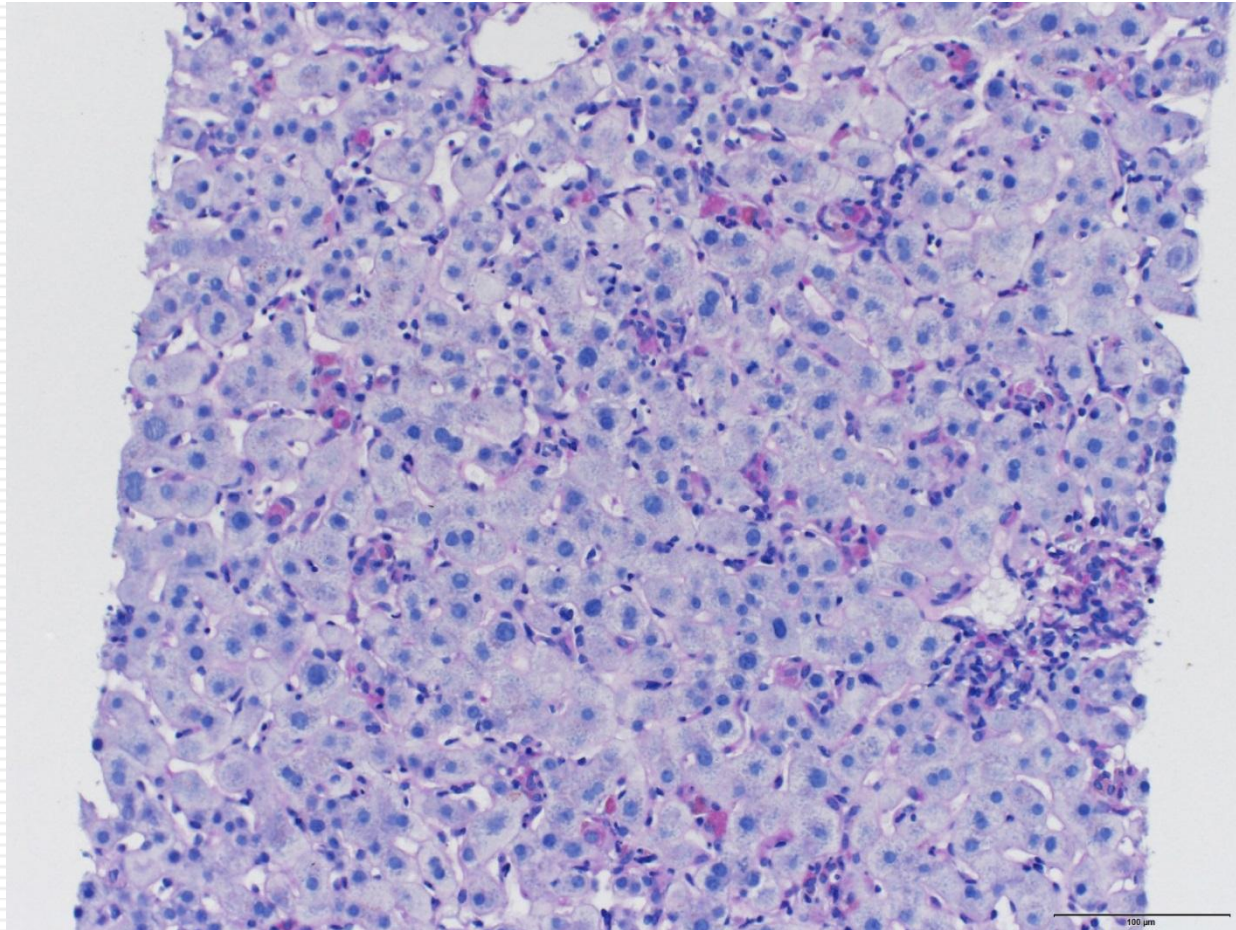
3



Lobular disarray and apoptotic bodies



Diffuse sinusoidal lymphocytic inflammation



Several mononuclear phagocytes with ceroid pigment

Laboratory

HCV Genotype 1a

Viral load 1'182'788 IU/mL

Serological test results were negative for HAV,
HBV, HDV and HEV, CMV and EBV

Diagnosis

Acute HCV hepatitis

Follow-up 6 months later:

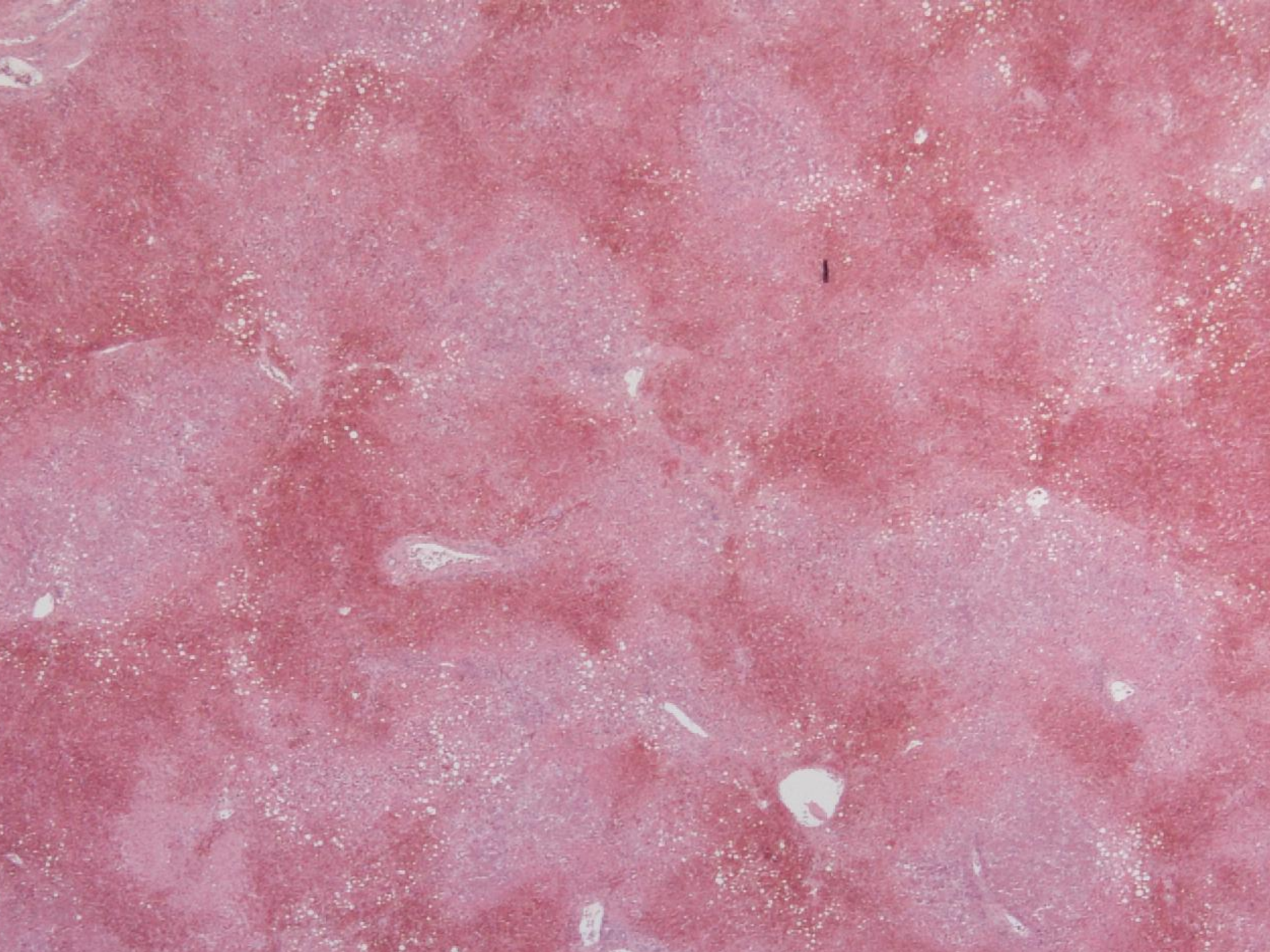
After initial normalization of LFTs and undetectable viral load, in December 2014 relapse of HCV viremia (viral load 2902 IU/ml) : chronic hepatitis

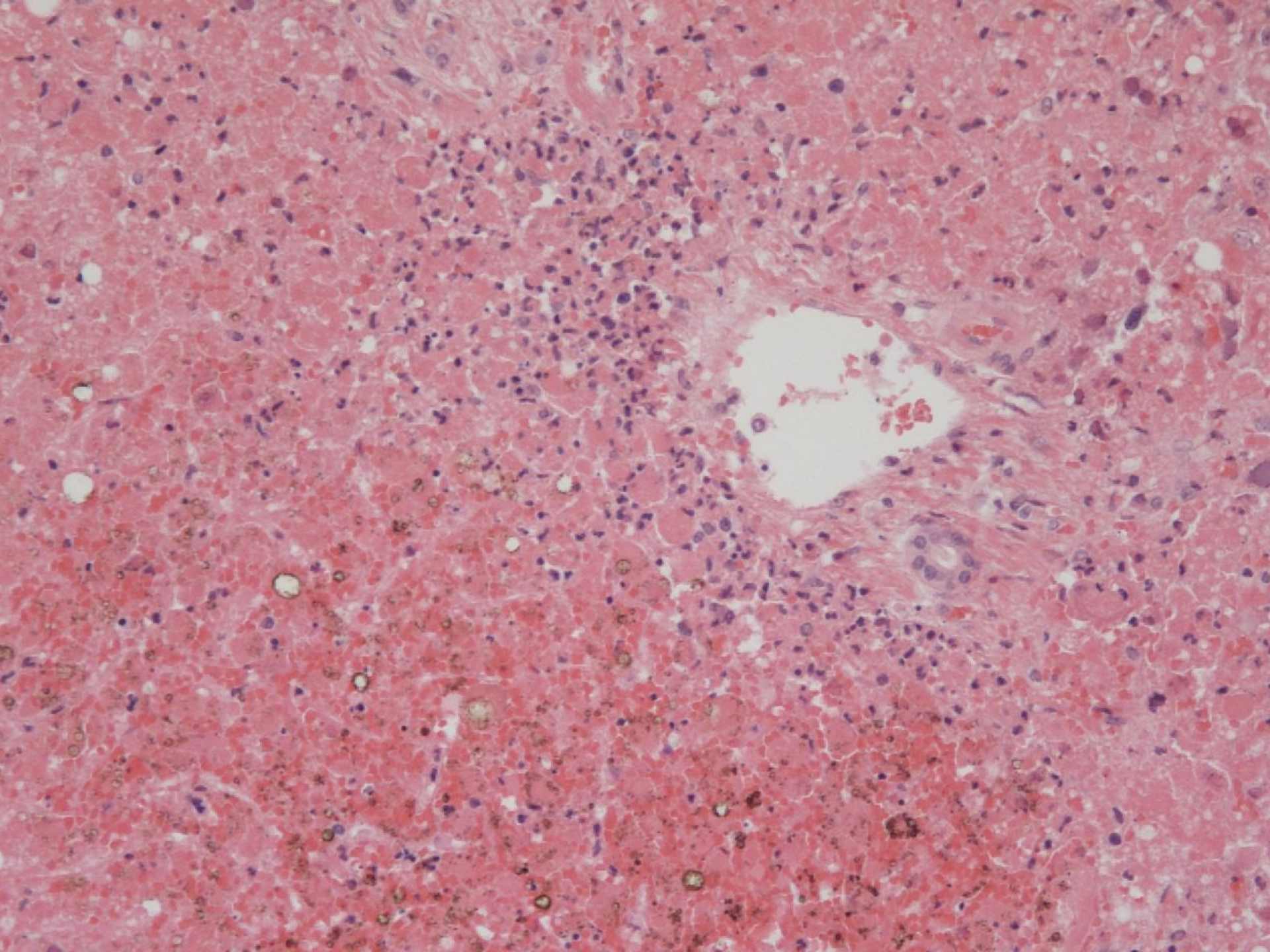
-
- Symptomatic acute HCV is very rare
 - Liver biopsy findings are very characteristic for acute HCV infection, but biopsy is not required in most cases

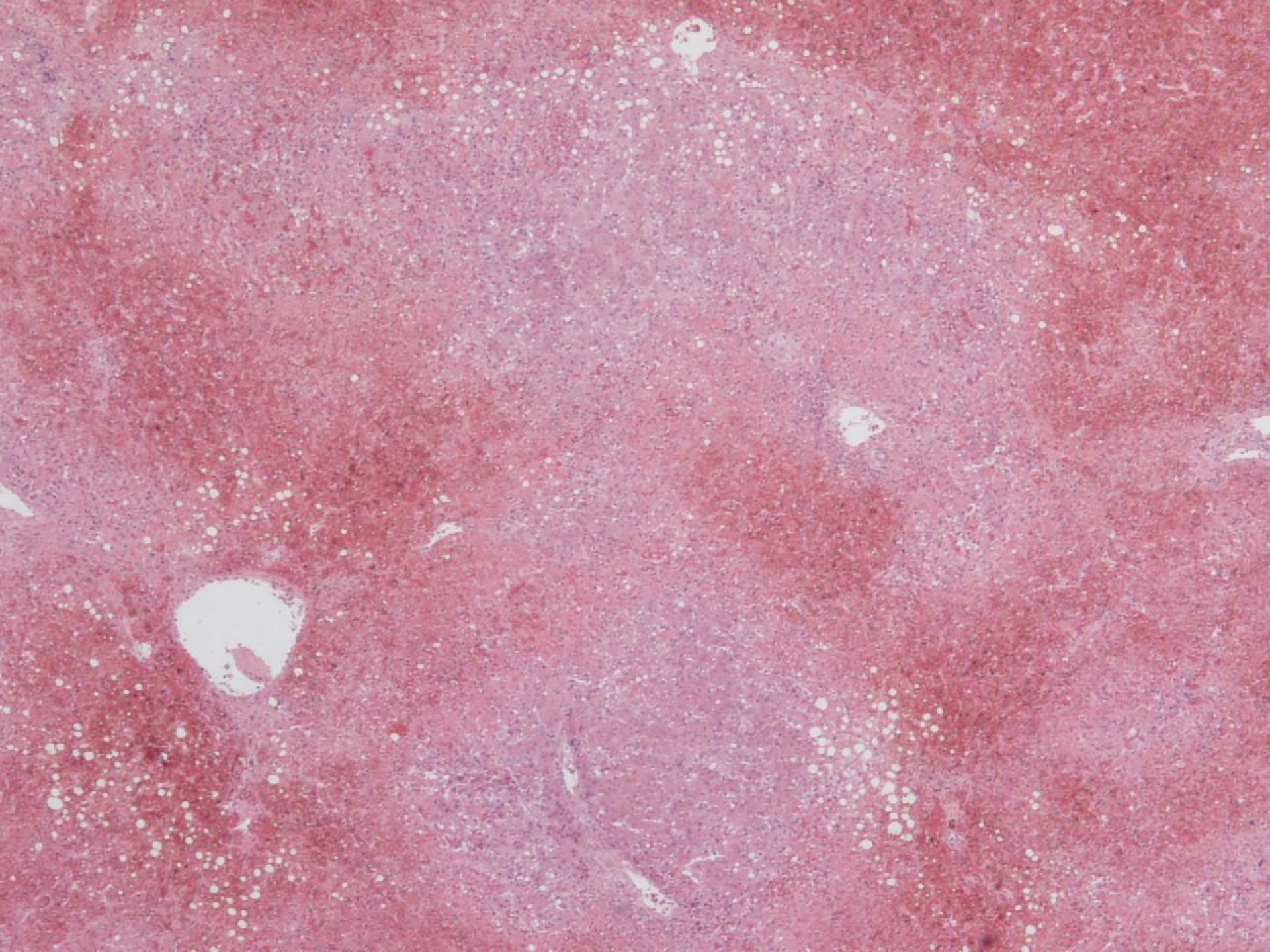
Birmingham B/2015

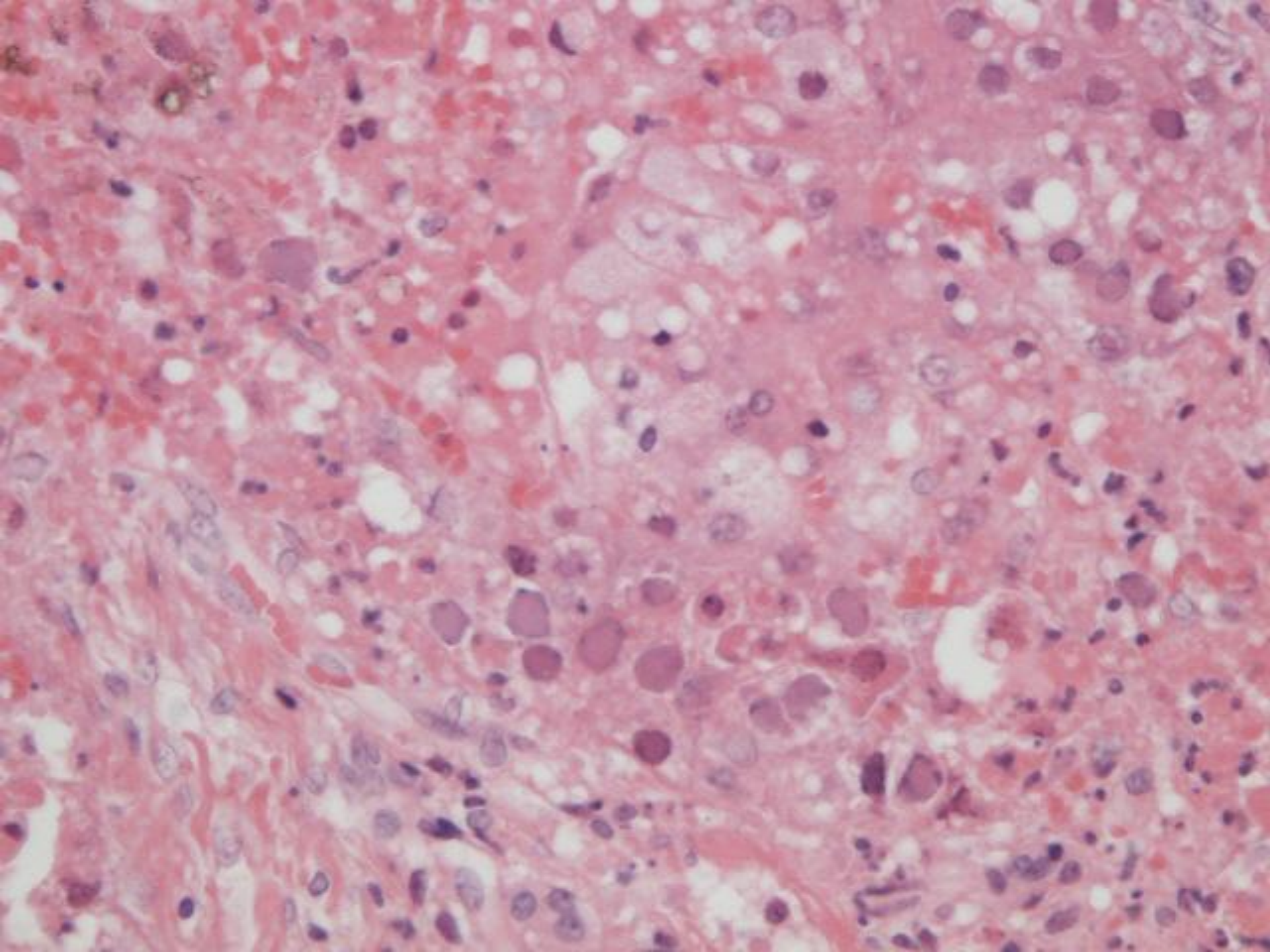
Female, age 38

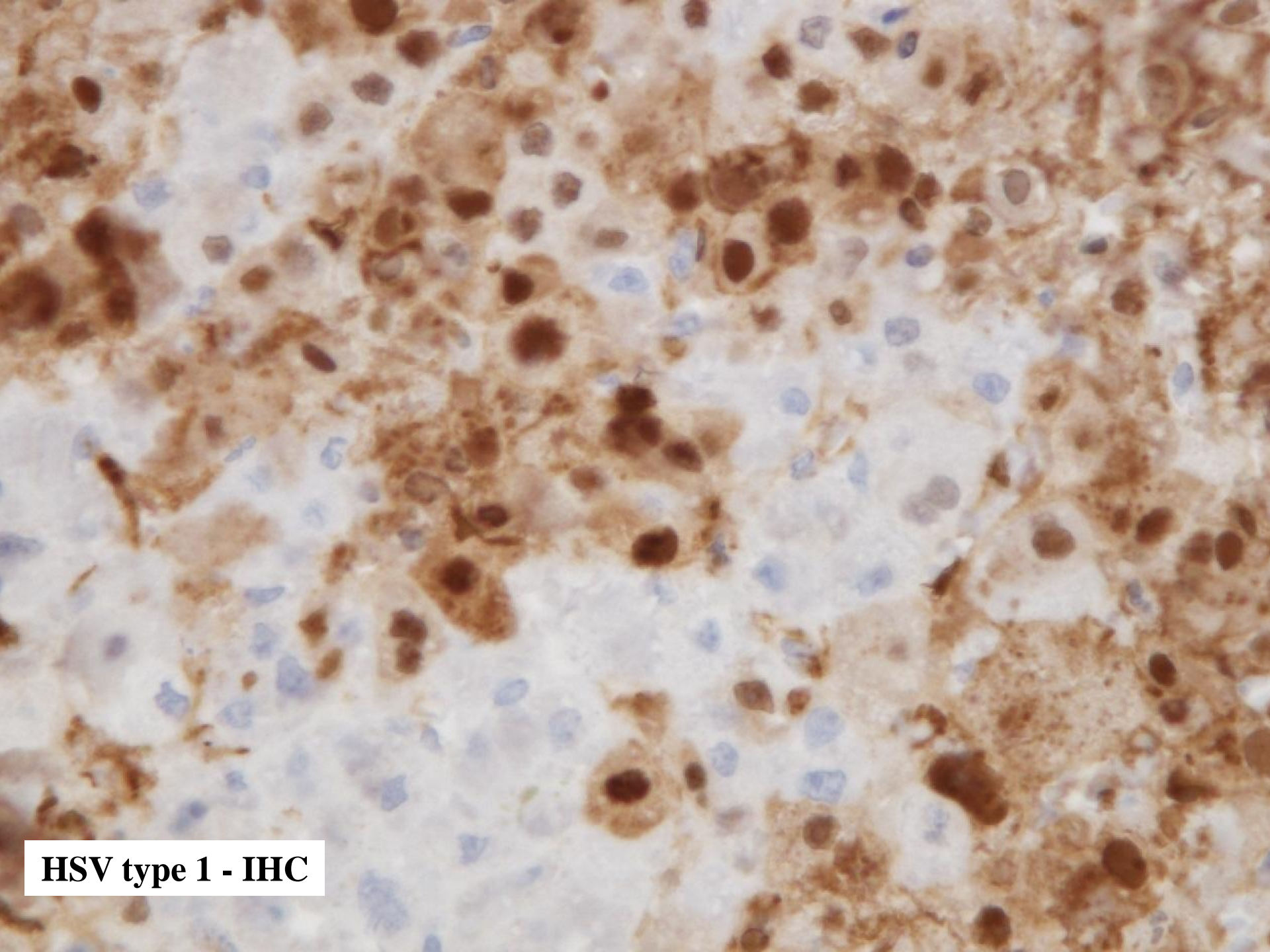
- Acute liver failure.
- Previous history of severe Crohn's disease, unresponsive to treatment.
- Taking paracetamol in large doses for abdominal pain.
- Presumed paracetamol overdose due to therapeutic misadventure.
- Underwent urgent liver transplantation.
- During operation, pupils became fixed and dilated. Died 12 hours post-transplant.
- Hepatectomy specimen weighed 1850g and showed zonal congestion, producing “nutmeg-like” appearance.











HSV type 1 - IHC

Birmingham B/2015 – Diagnosis

1. Severe herpes simplex hepatitis virus hepatitis, with extensive hepatocyte necrosis
 - ? Secondary to immunosuppressive therapy for Crohn's disease
2. Has paracetamol toxicity contributed to liver damage?
 - Extensive hepatic necrosis could be related to HSV hepatitis alone

Herpes Simplex Hepatitis

- Mainly a disease of neonates and young children
- Rare in adults (< 1% of cases of acute liver failure)
- Most cases occur in setting of defects in cell mediated immunity
 - e.g. post-transplant, steroid therapy, pregnancy
- Some occur in apparently immunocompetent individuals
 - 15 – 24% had no predisposing cause (Kaufman 1997, Norvell 2007)
- Approximately 60% have cutaneous/oral/genital lesions
- Most cases are not diagnosed until death
 - Correct pre-mortem diagnosis in 23 - 42% (Kaufman 1997, Norvell 2007)
- Early diagnosis and treatment with acyclovir may improve outcome
 - Liver biopsy is “gold standard” for diagnosis

Acute Liver Injury – Circulated Cases

1. VIRAL (n = 8)

a) Hepatotropic

- HCV – Basel A

b) Non-hepatotropic

- EBV – Vienna A, NCL –B (?)
- Enterovirus – Rome A
- Dengue – Paris A
- Herpes simplex – Bham B, Leuven A
- HHV6 - STL A (?)

Causes of Acute Hepatitis / Acute Liver Injury

1. Viral Hepatitis
2. Drugs
3. Autoimmune (alloimmune) hepatitis
4. Other

Brisbane B

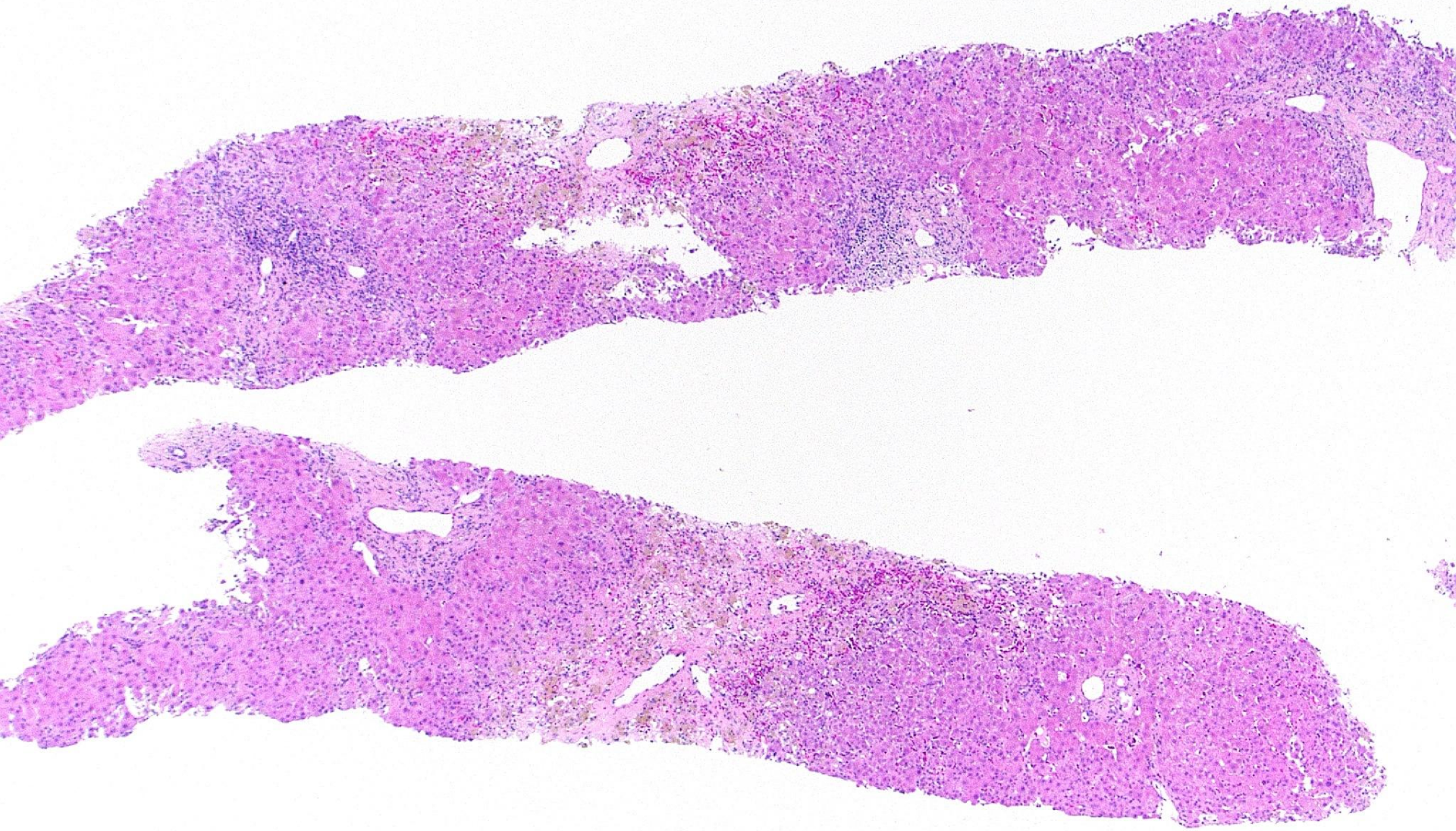
(Andrew Clouston)

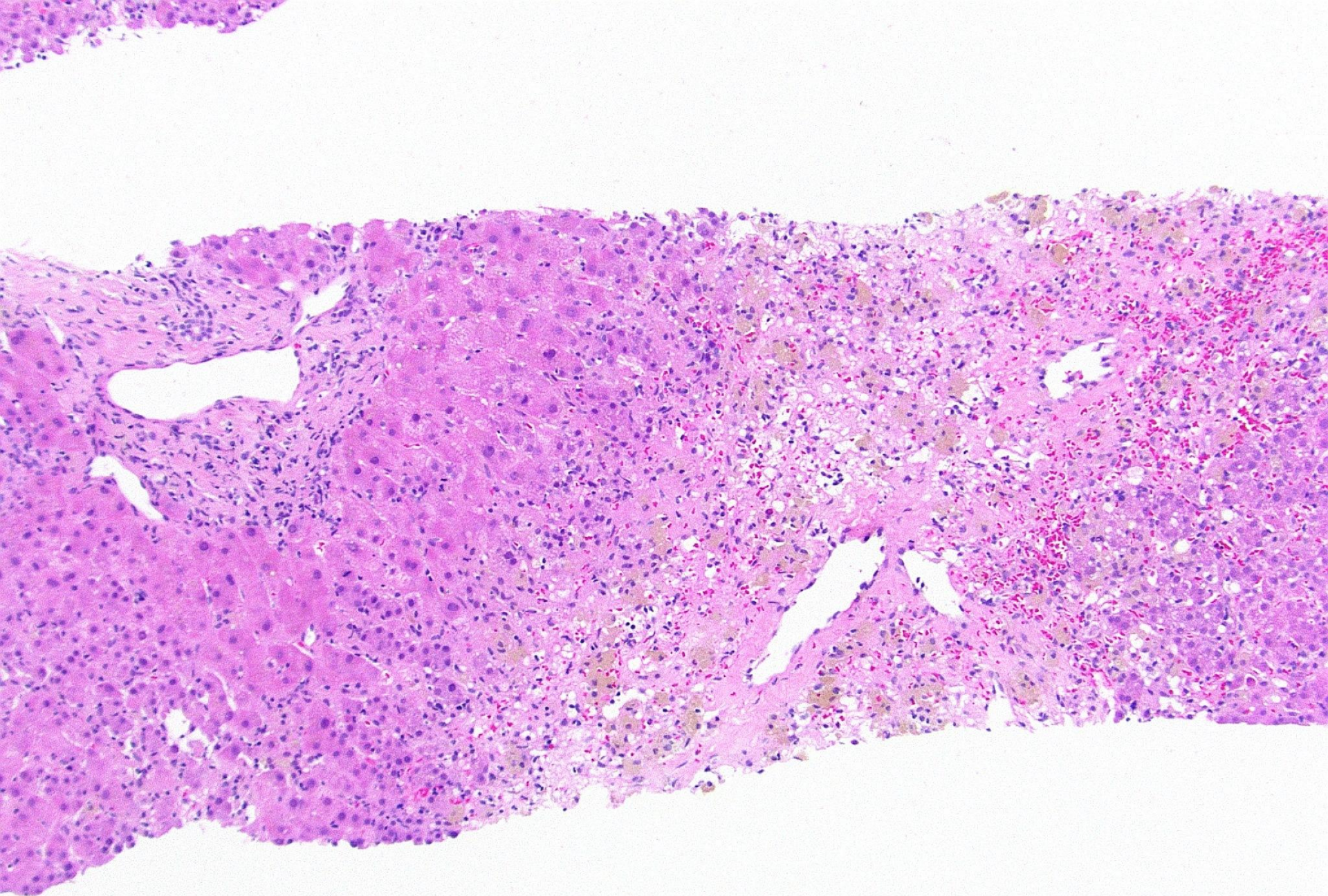
54 year old female (Asian) with known likely HCC

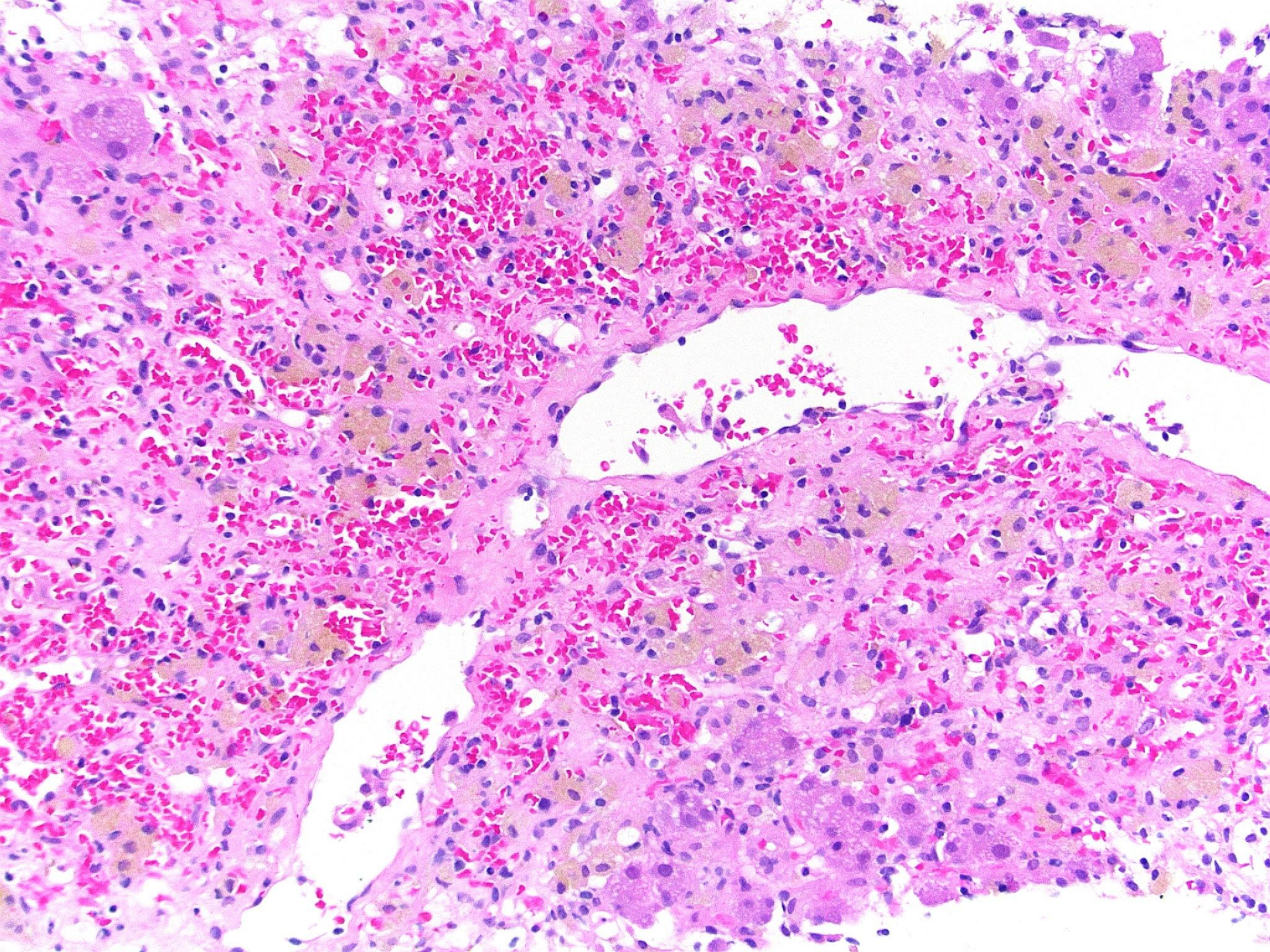
- 7cm mass R liver. AFP 6200
- Also lung mets

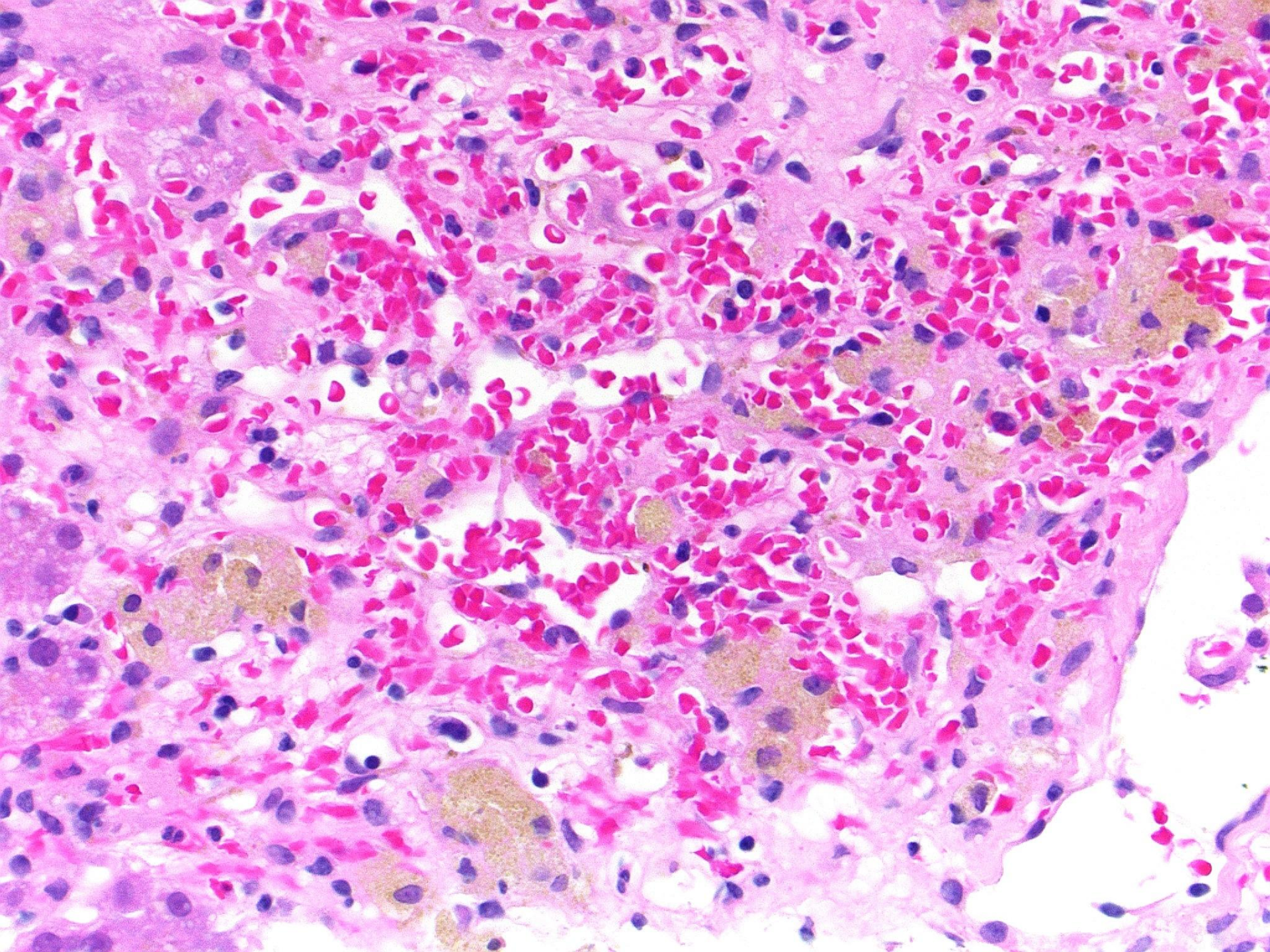
Treated with Sorafenib.

Sudden fulminant hepatitis. ?drug.









Sorafenib hepatotoxicity

- up to half have increased ALT/AST (6-53%)
- 1-3% transaminases > 5 x ULN
- case reports of severe hepatitis / liver failure
 - most cases occurred in patients with cirrhosis
 - but 1 patient Rx for RCC died
- onset few days to 8 weeks
- mechanism of liver toxicity uncertain
- metabolised by CYP 3A4 (centrilobular hep)

Adelaide B – Alastair Burt

- 59 year old female presented with jaundice, fatigue and features of mild encephalopathy (? duration of 'a few weeks')
- Periods of heavy drinking (> ½ bottle spirits/day)
- Autoantibodies and viral screen negative
- Imaging investigations show small shrunken liver
- Liver transplantation

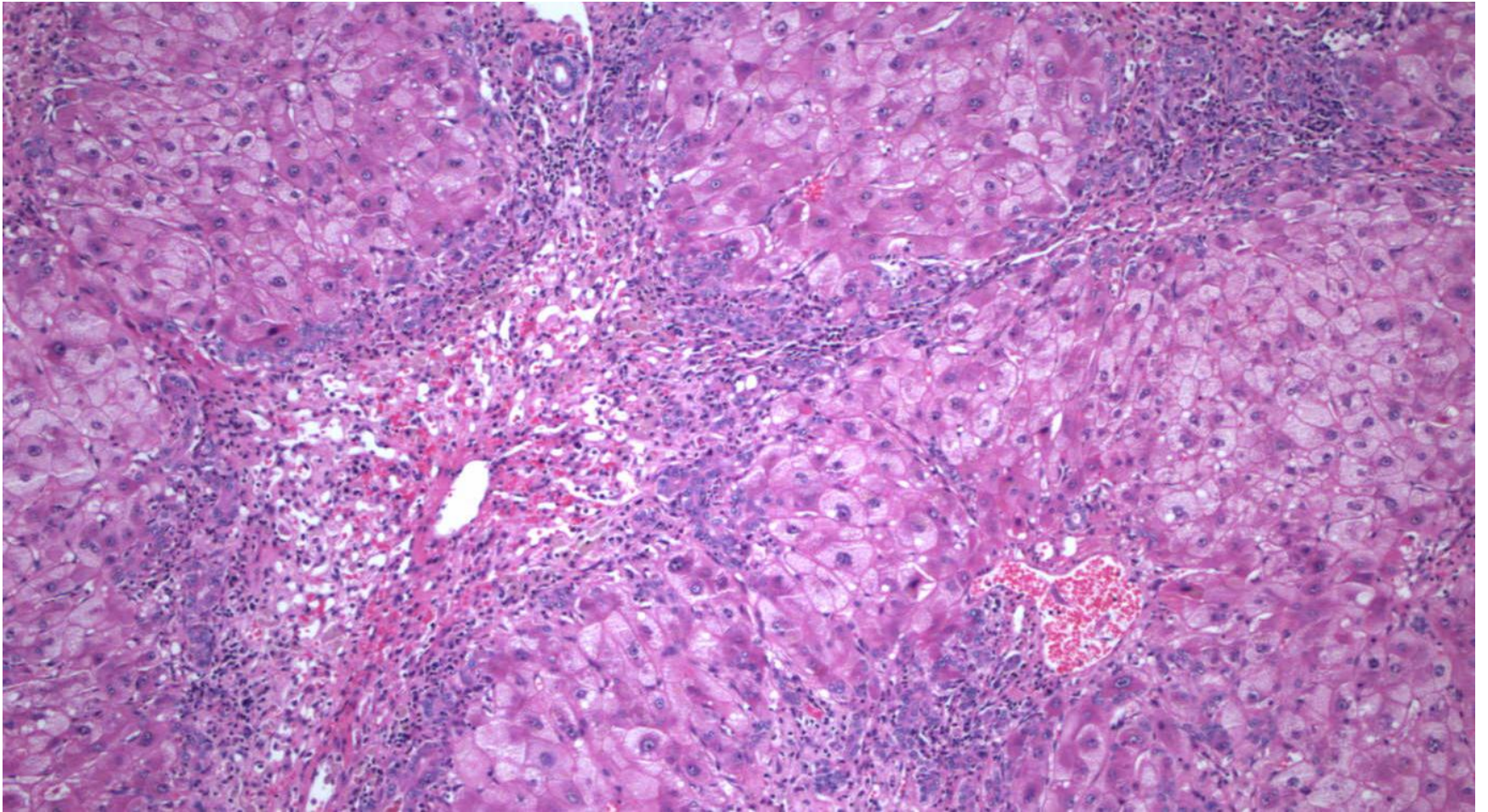
Adelaide B

- Referred case: “could you please let us know what you think the likely aetiology of this cirrhosis is?”
- “Probable biliary cirrhosis” : marked ductular reaction

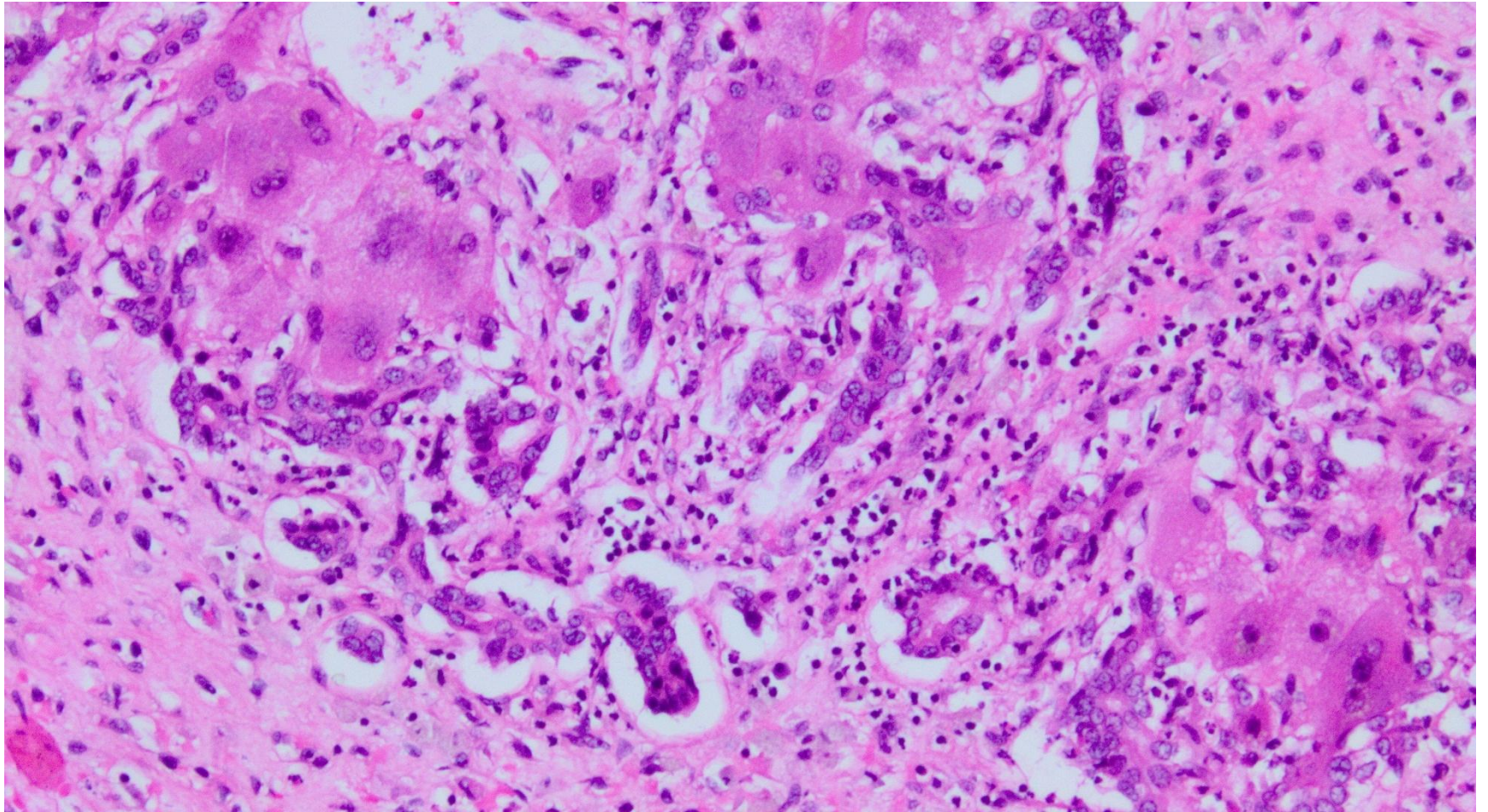
Adelaide B



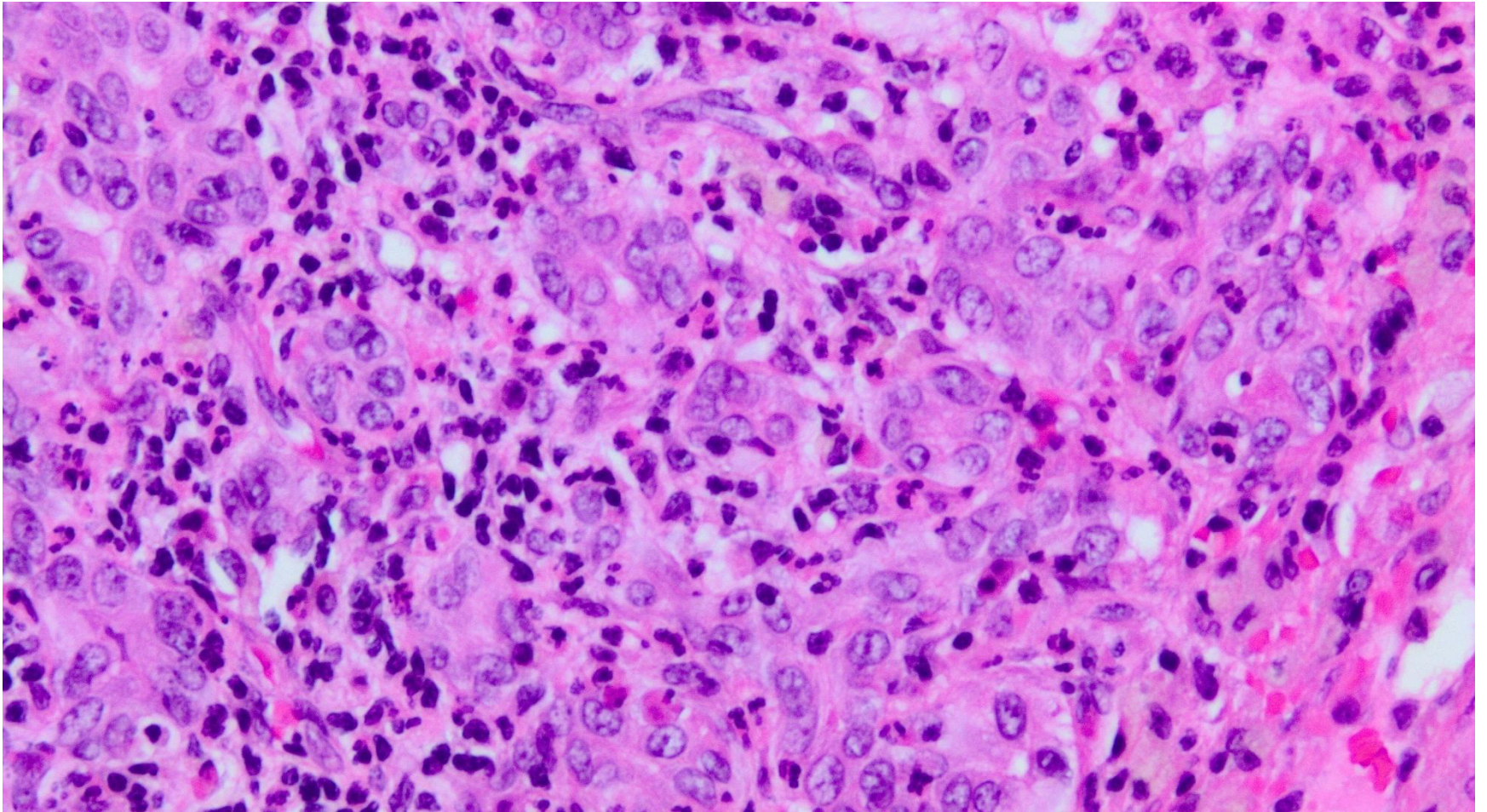
Adelaide B



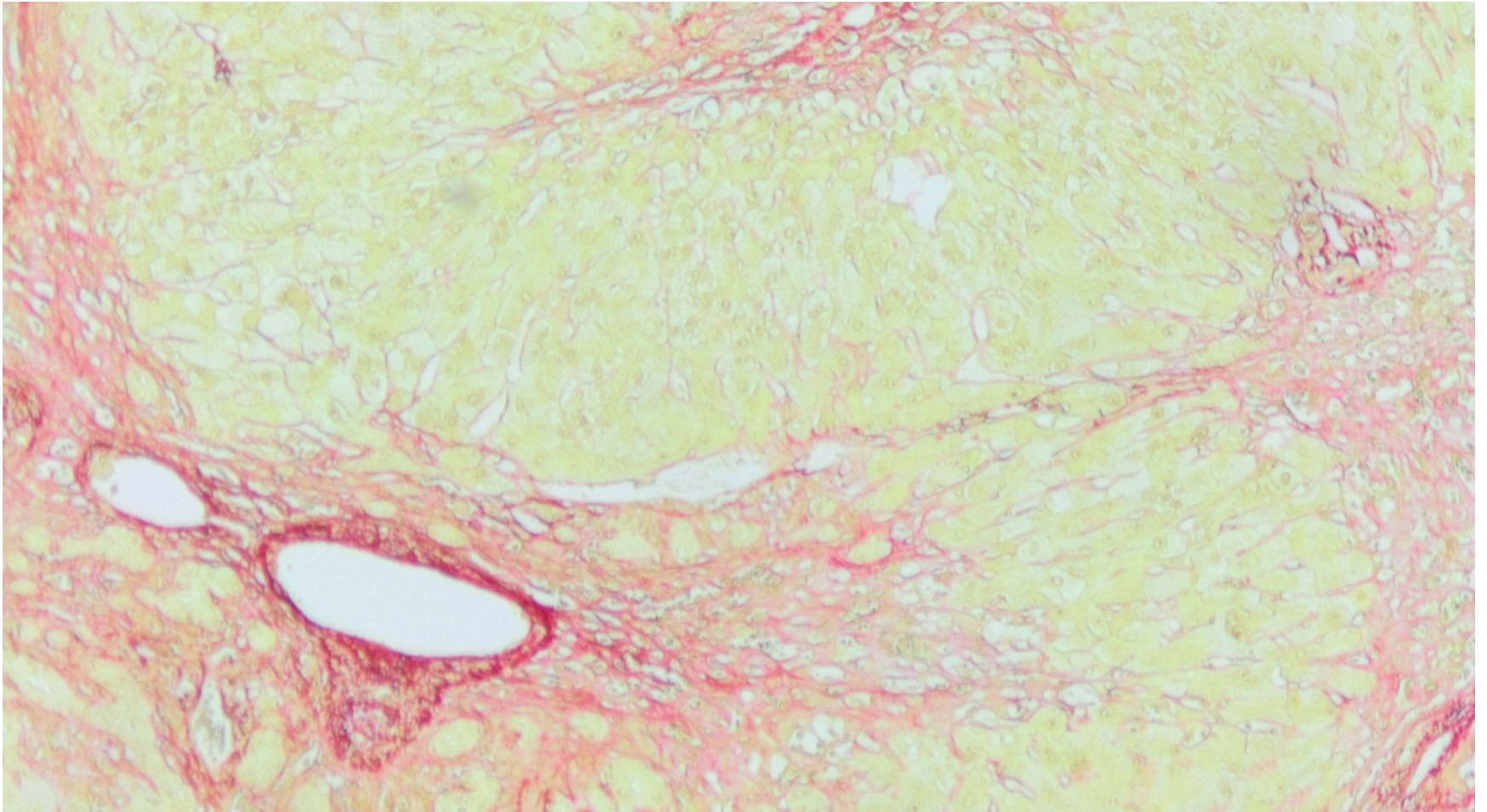
Adelaide B



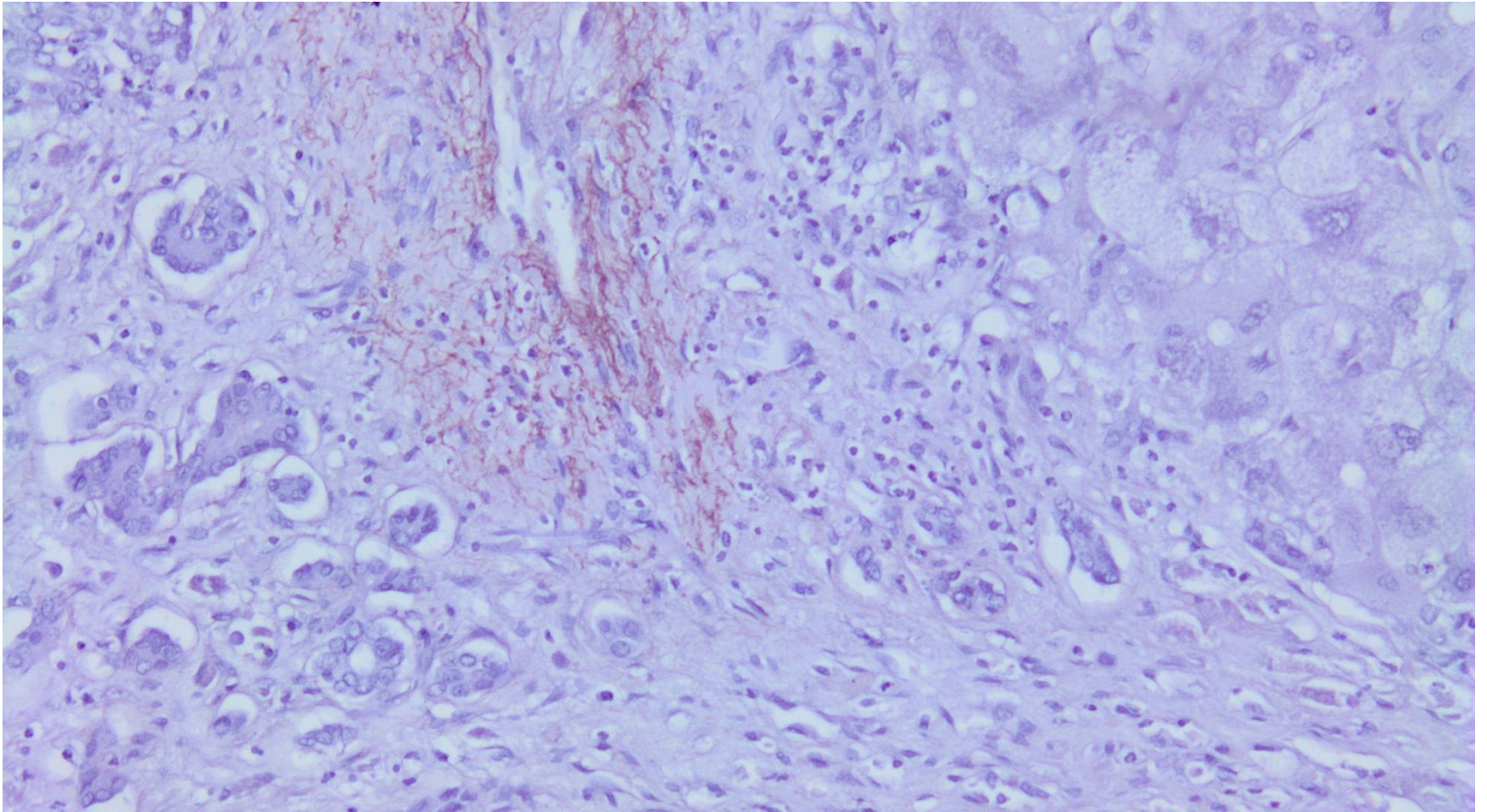
Adelaide B



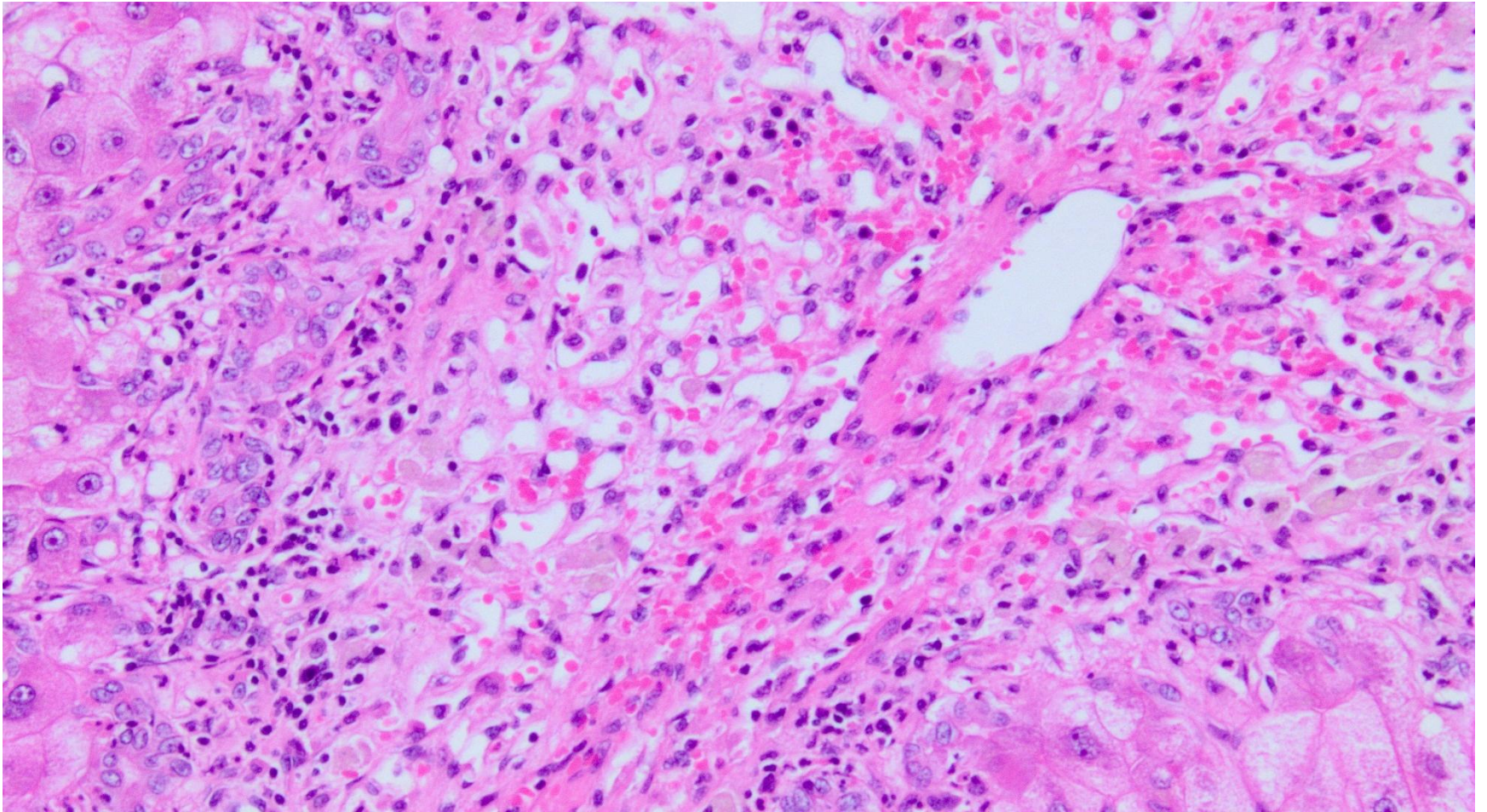
Adelaide B



Adelaide B



Adelaide B



Adelaide B

- No evidence of chronic liver disease!
- Confluent zone 3/2 necrosis with bridging
- Ductular reaction: response to necrosis
- No 'hepatitis'
- No viral inclusions

Adelaide B

- Further history!
- Recent episodes of backache
- ++ analgesic use combined with continued heavy alcohol intake
- Includes paracetamol (acetaminophen) containing preparations
- Remains inconclusive but no other toxins identified so probable therapeutic misadventure

Acetaminophen and therapeutic misadventure

- First identified by Wright and Prescott (1973) in Scottish Medical Journal
- Seeff et al (1986): described 6 cases and reviewed 19 in literature of chronic alcoholics who developed severe hepatotoxicity with apparently moderate doses
 - Alcohol causes induction of CYP 450 and depletion of glutathione
- Definitive paper by Zimmerman and Maddrey (1995): 67 alcoholic patients taking APAP with therapeutic intent leading to liver injury – 20% mortality (similar features to 94 cases reviewed from the literature)
- Concept challenged by Makin & Williams (2000)
 - Most cases taking doses significantly above therapeutic range
 - No difference in paracetamol related toxicity in heavy drinkers versus non – drinkers
 - More appropriate to describe as ‘accidental overdose’

Acute Liver Injury – Circulated Cases

2. DRUGS (n = 4)

- Methylprednisolone – Halifax A
- Black cohosh – Brisbane A
- Sorafenib – Brisbane B
- Paracetamol (accidental OD) – Adelaide B

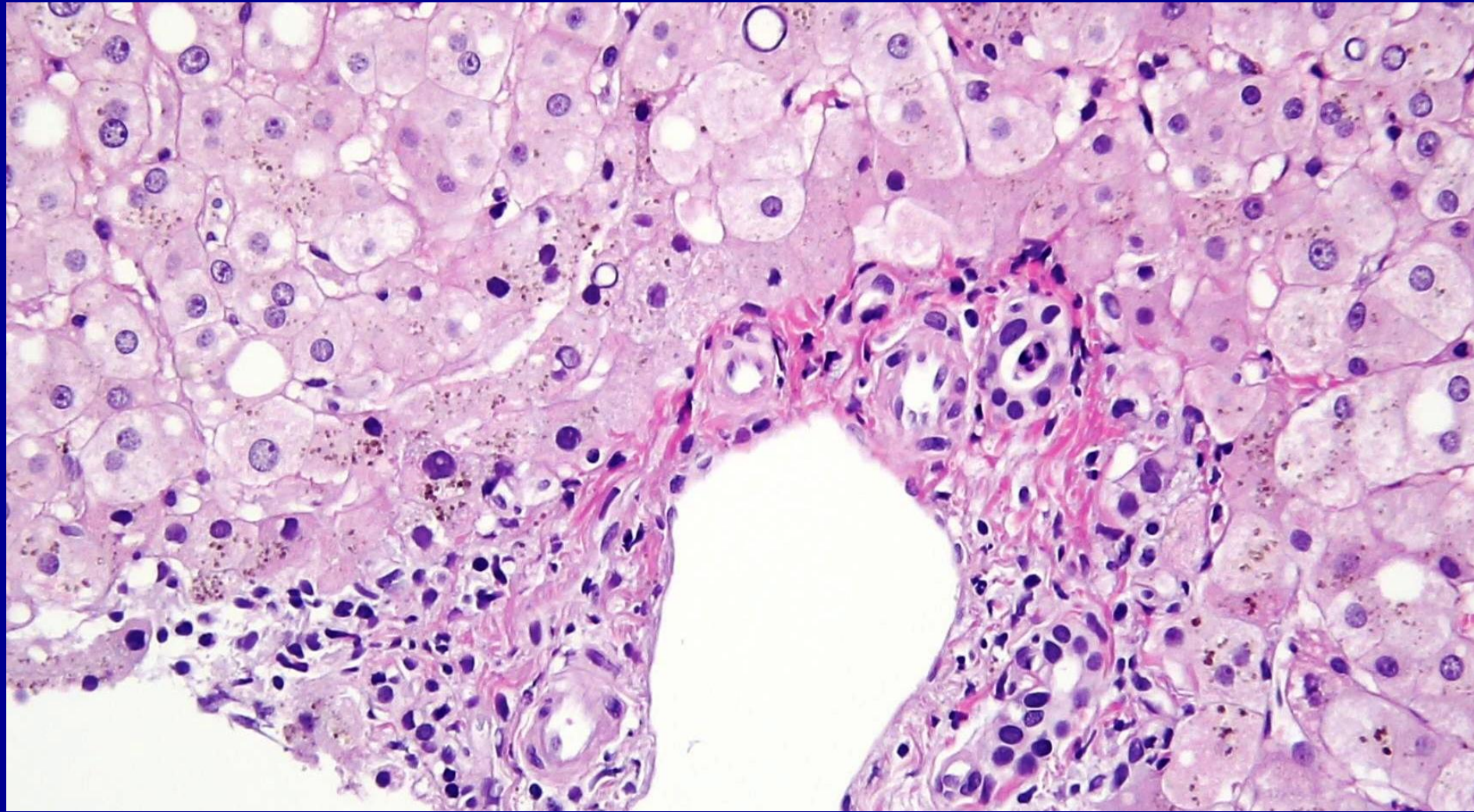
Causes of Acute Hepatitis / Acute Liver Injury

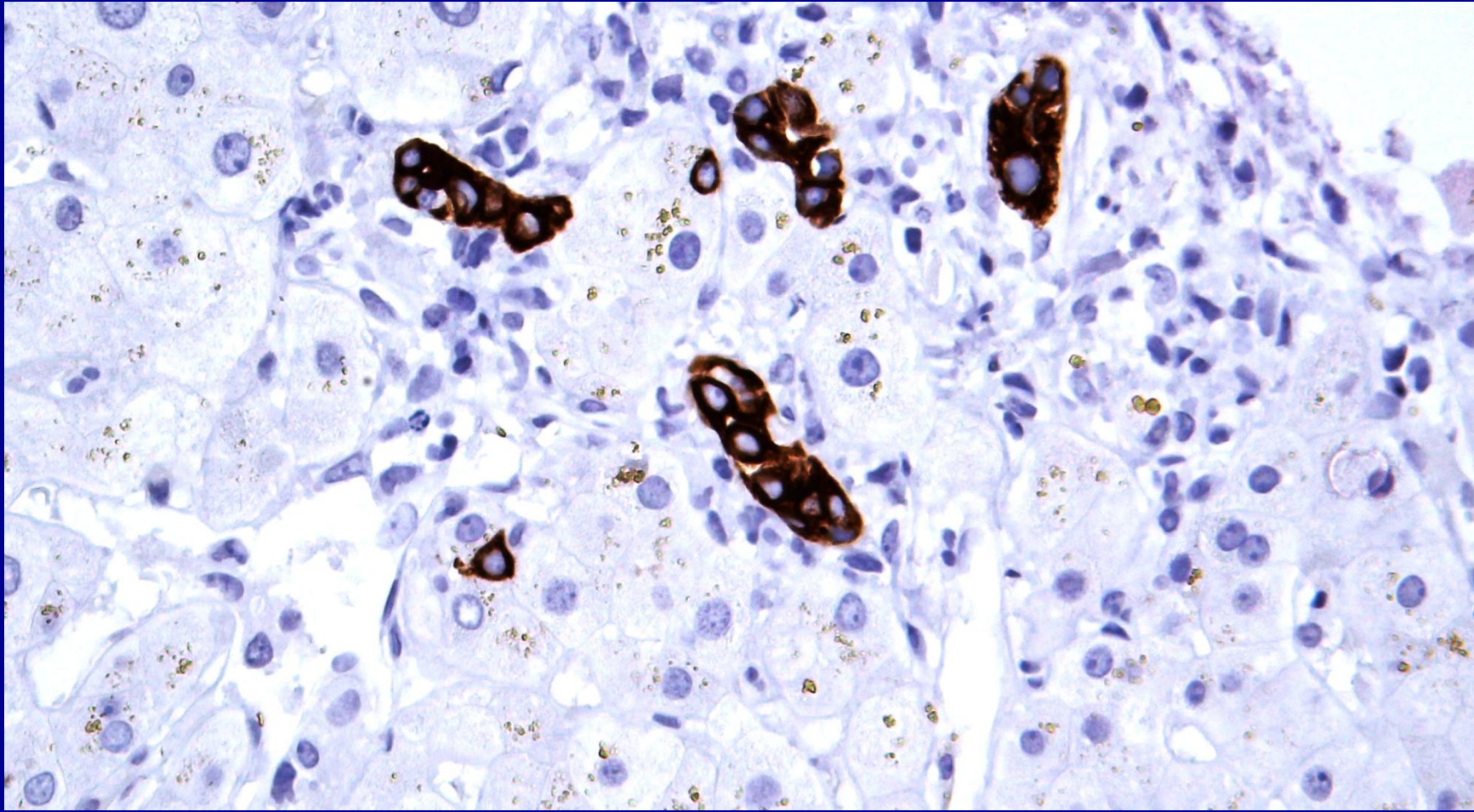
1. Viral Hepatitis
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4. Other

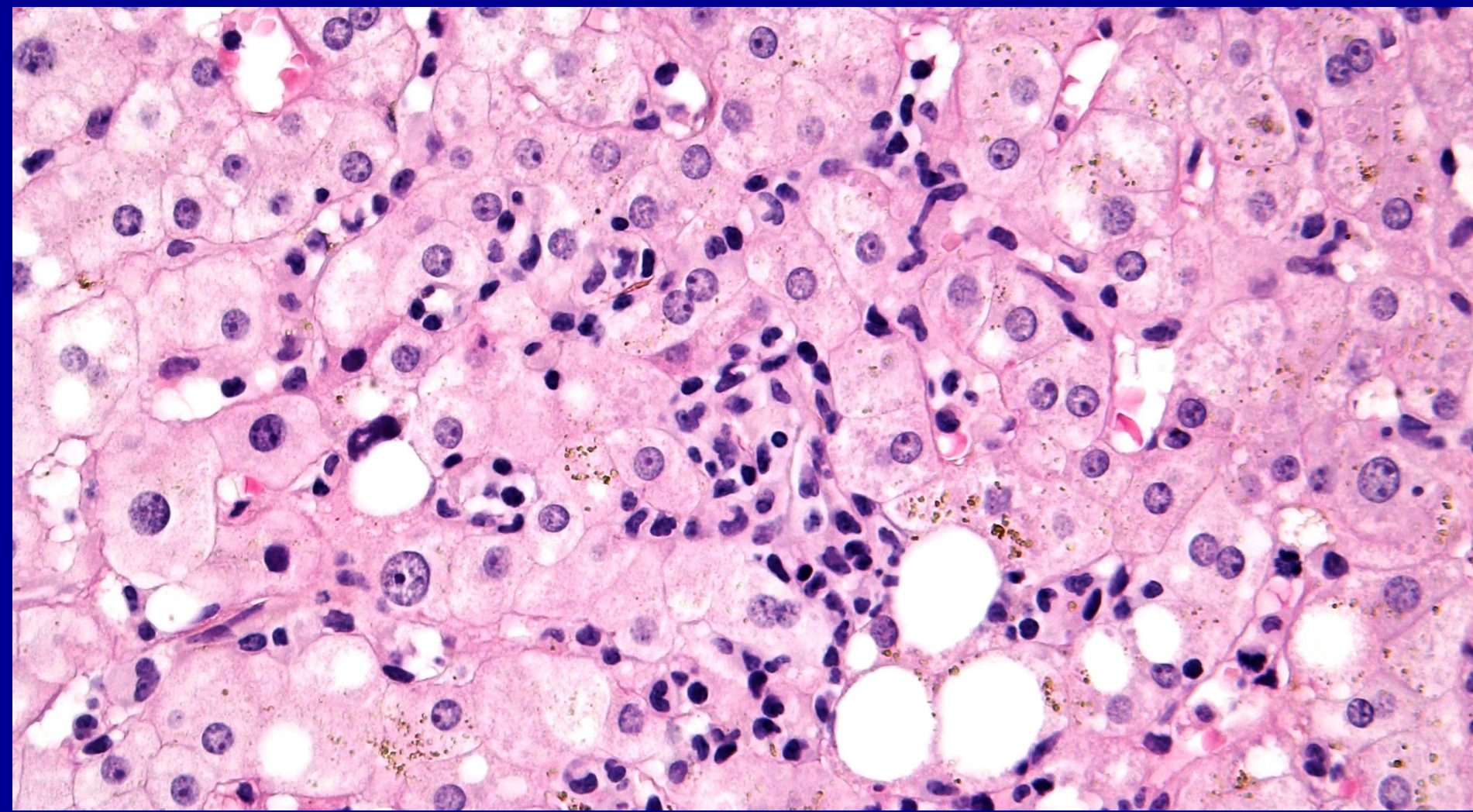
Groningen B – Annette Gouw

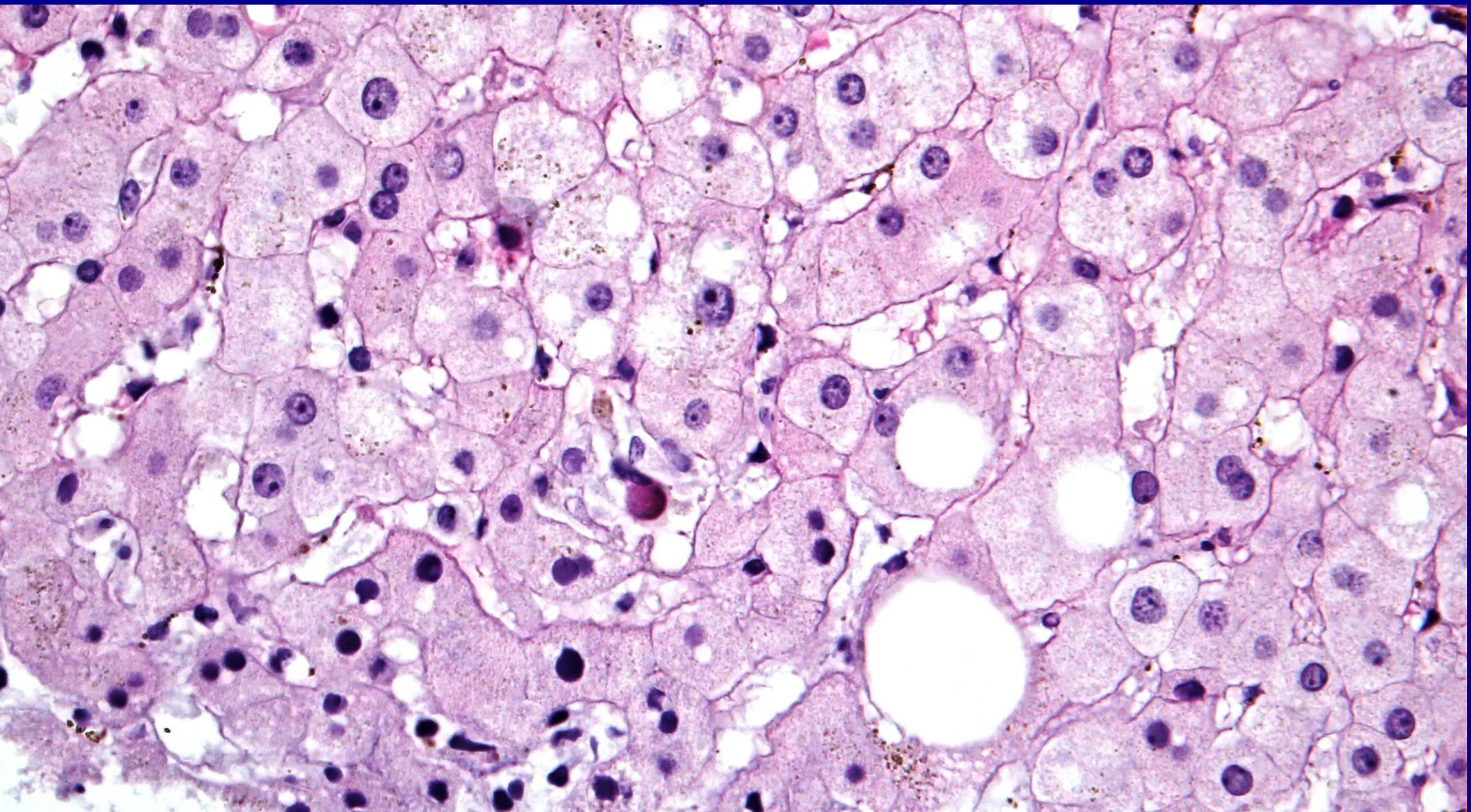
- Male patient 35 yrs.
- 2009: myelodysplastic syndrome – RAEB/AML, chemotherapy.
- 2010: stem cell Tx matched unrelated donor
- 2013: recurrence, chemotherapy
- 2014: 2nd stem cell transplant.

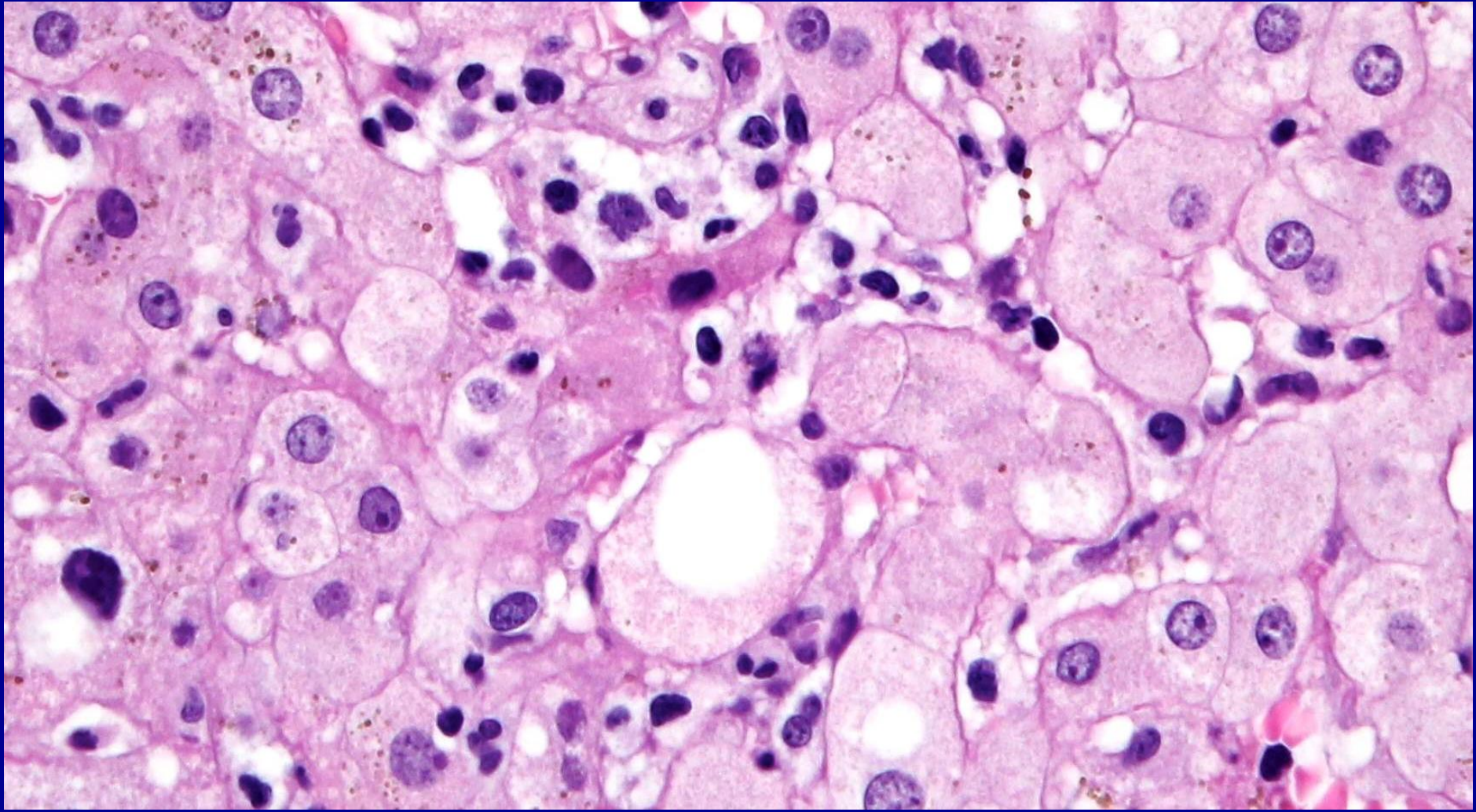
- One week before arrival in hospital fatigue, nausea, vomiting, no fever, no diarrhea, no skin abnormalities
- LFTs: AST 120, ALT 165, Total bilirubin 56umol/l (3.2 mg/dL), GGT 174, APh 136.
- Liverbx at day 46 after 2nd SCtx











Histological findings

- Mild bile duct damage, no DR, no ductopenia
- Mild Lobular inflammation, apoptotic hepatocytes
- Dx: Hepatitic GVH
- Pt responded well to steroids

Significance of lobular inflammation in GVHD

- Lobular inflammation seen in 77% of 48 bx with GVHD; significant LI → “hepatitic” in 25% (Quaglia 2007)
- AH: acute stage, preceding more obvious BD damage
- More commonly seen in association with typical bile duct changes (Strasser 2000)
- Distinction from other causes of lobular hepatitis (e.g. viral, drugs) important.
- Lobular Inflammation has prognostic value: high LI better prognosis, probably due to response to steroid treatment (Duarte 2005).

Acute Liver Injury – Circulated Cases

3. AUTOIMMUNE (ALLOIMMUNE) HEPATITIS (n=4)

a) Autoimmune

- AIH-PBC – Halifax B

b) Alloimmune

- Neonatal haemochromatosis – Rochester A, Rome B
- Hepatitic GVHD – Groningen B

Causes of Acute Hepatitis / Acute Liver Injury

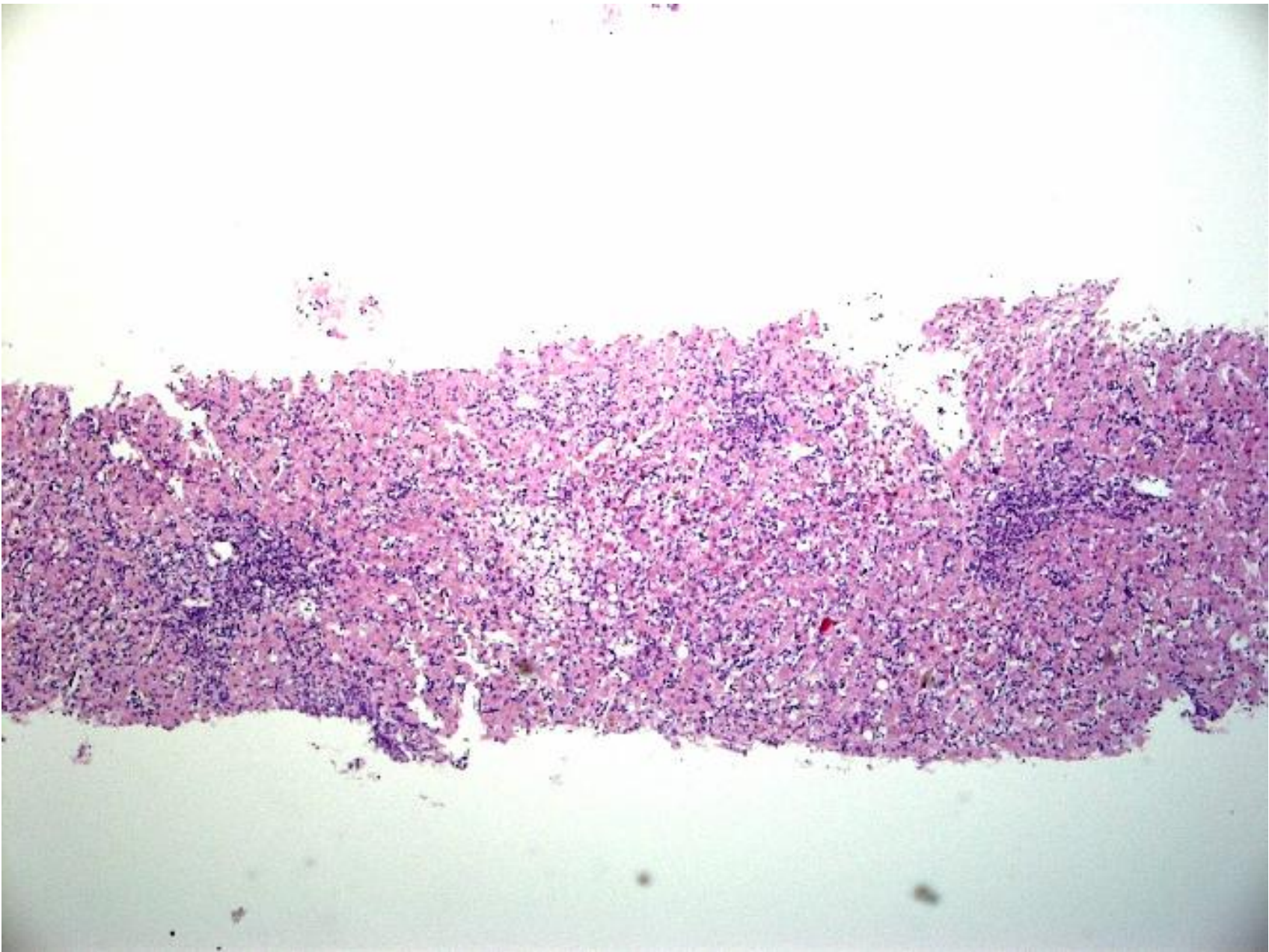
1. Viral Hepatitis
2. Drugs
3. Autoimmune (alloimmune) hepatitis
4. **Other**

Vienna Case B – Hans Dienes

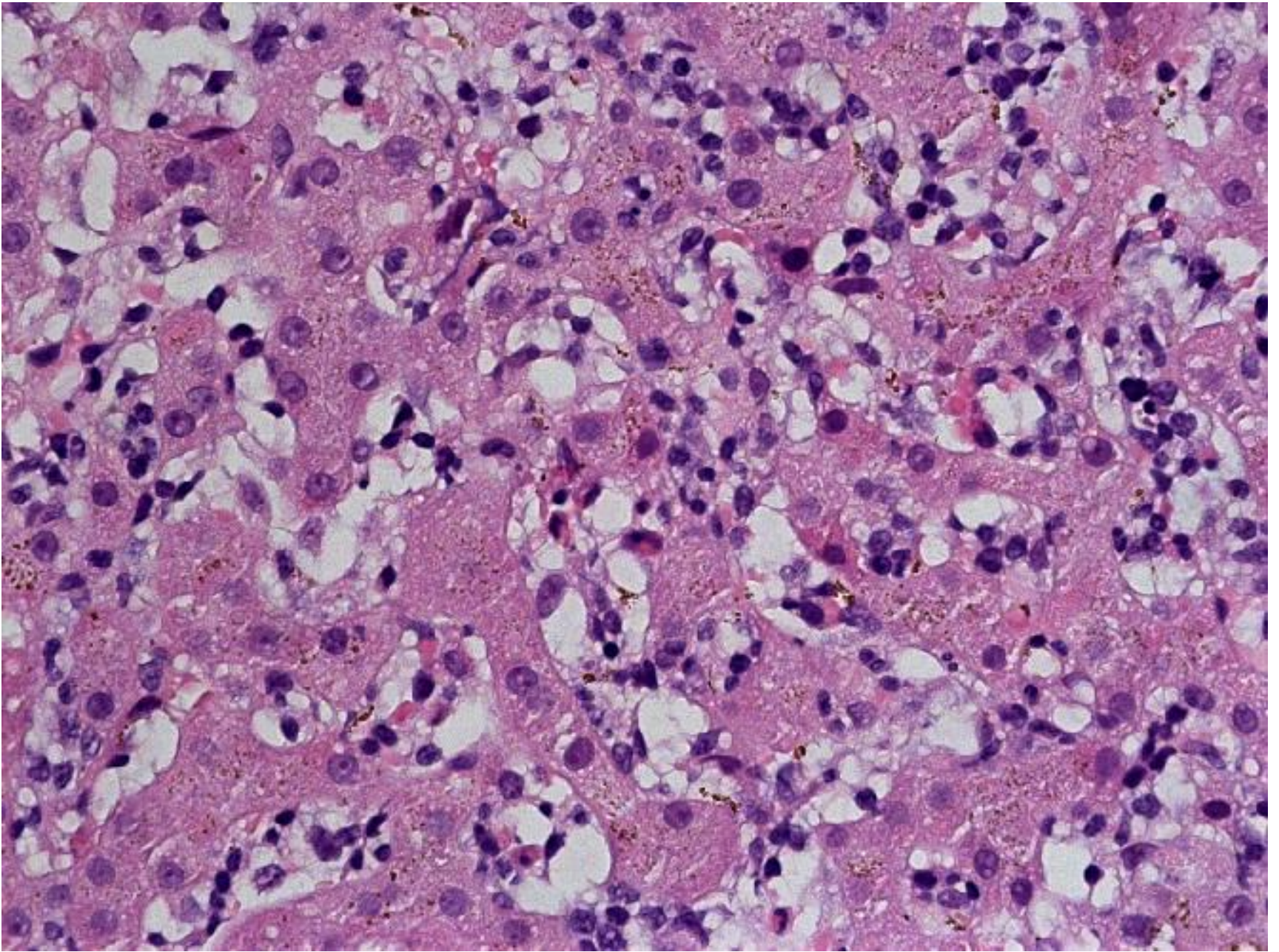
Male patient ,51 y old with abdominal pain and hepatosplenomegaly.

Transaminases were 3 times upper normal limit.

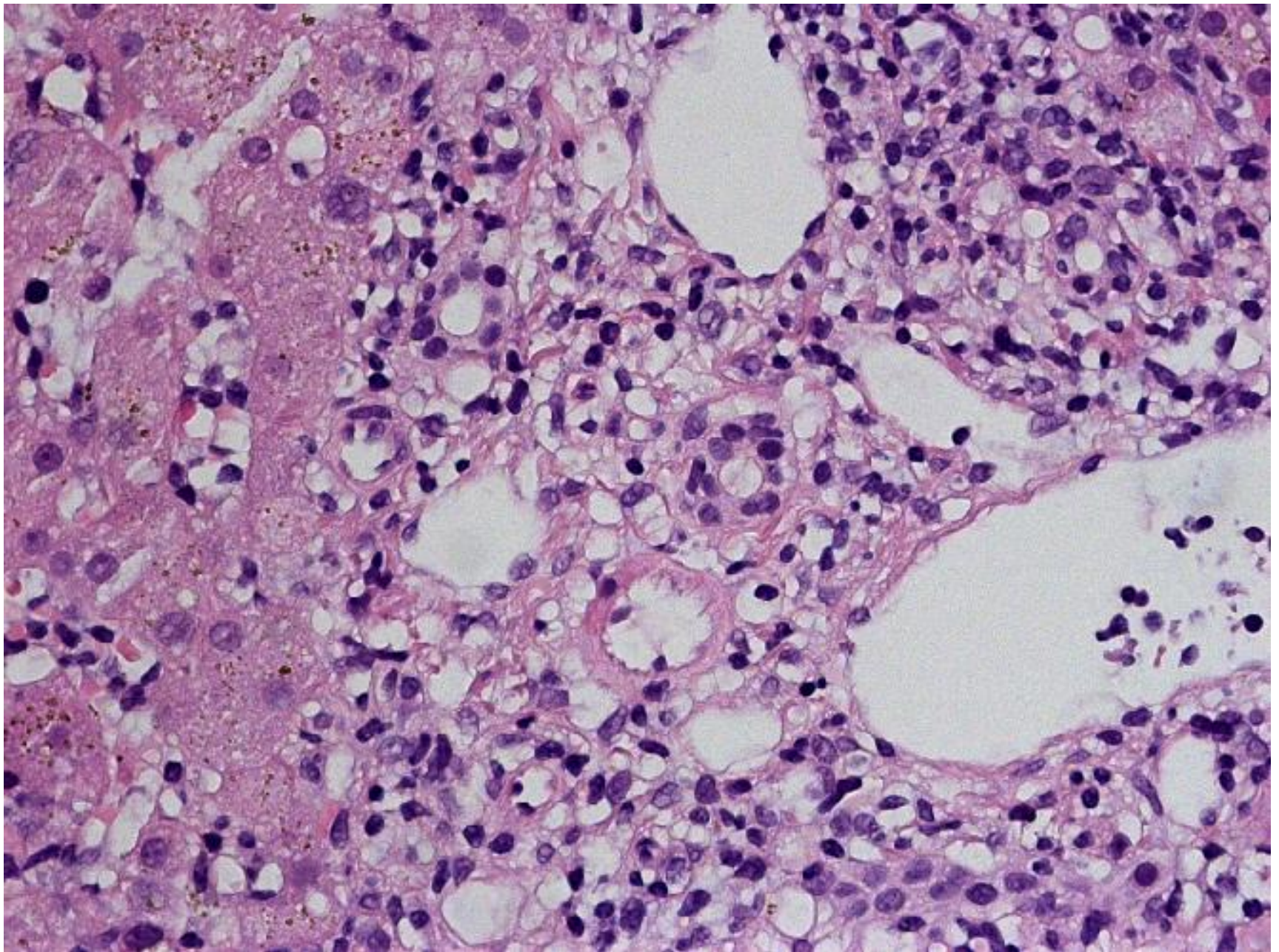
**The patient was under treatment for T cell lymphoma, and clinicians asked for
drug-induced injury**



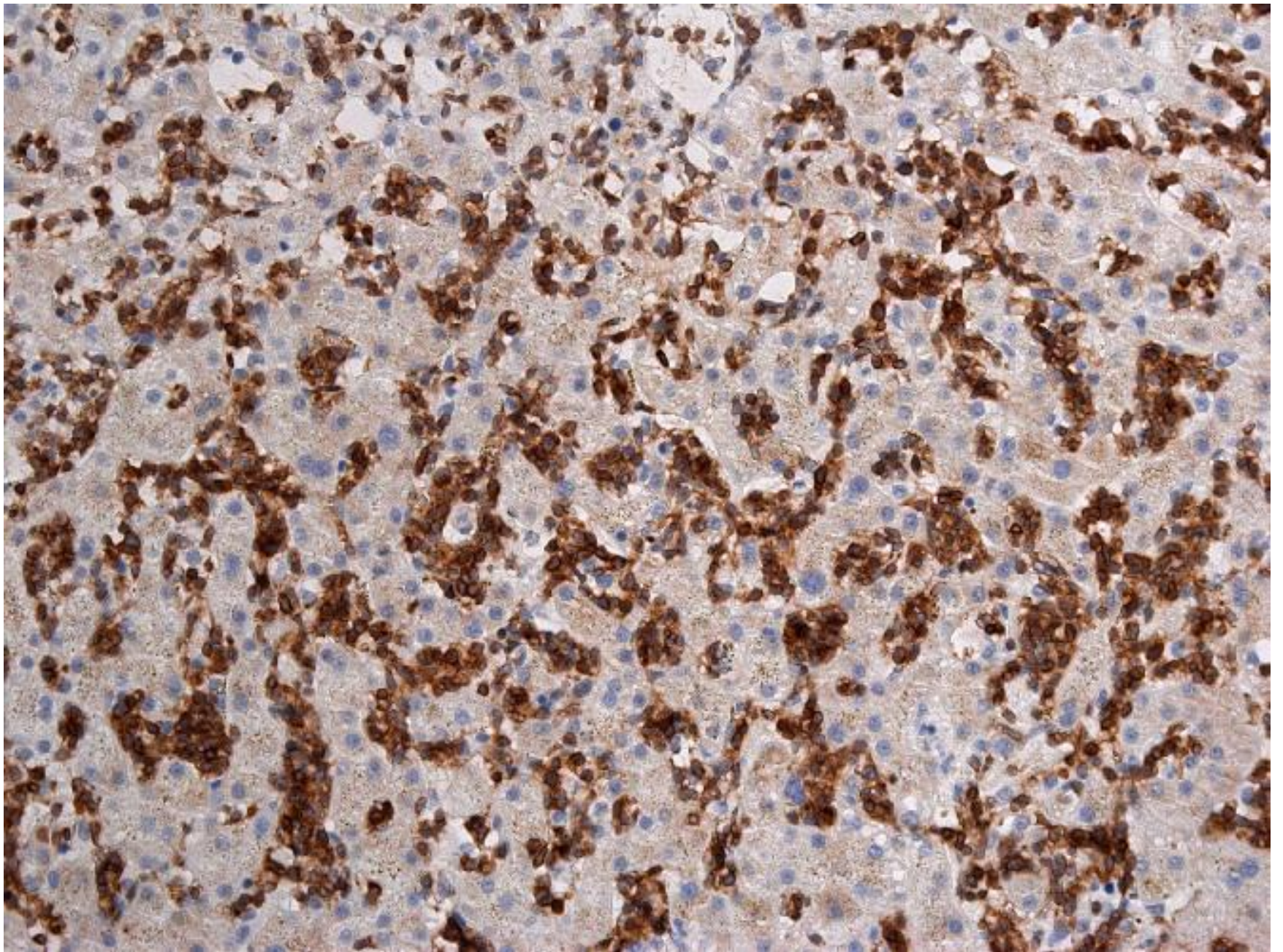
Vienna Case B HE



Vienna Case B HE



Vienna Case B HE



Vienna Case B CD3



Vienna Case Ki 67

Vienna Case B

**Diagnosis: Infiltration by
Hepatosplenic T Cell
Lymphoma**

Neoplastic infiltration presenting as fulminant acute liver failure

Prevalence/Clinical Presentation

- Uncommon – 18/4020 (0.44%) admissions for acute liver failure KCH London (Rowbotham 1998)
- In some cases acute liver failure may be the presenting feature of otherwise undiagnosed malignancy (usually leukaemia/lymphoma)

Aetiology

- Usually lymphoma (including primary hepatic lymphoma)
- Less commonly carcinoma/other
e.g. breast, lung (small cell carcinoma), melanoma, prostate

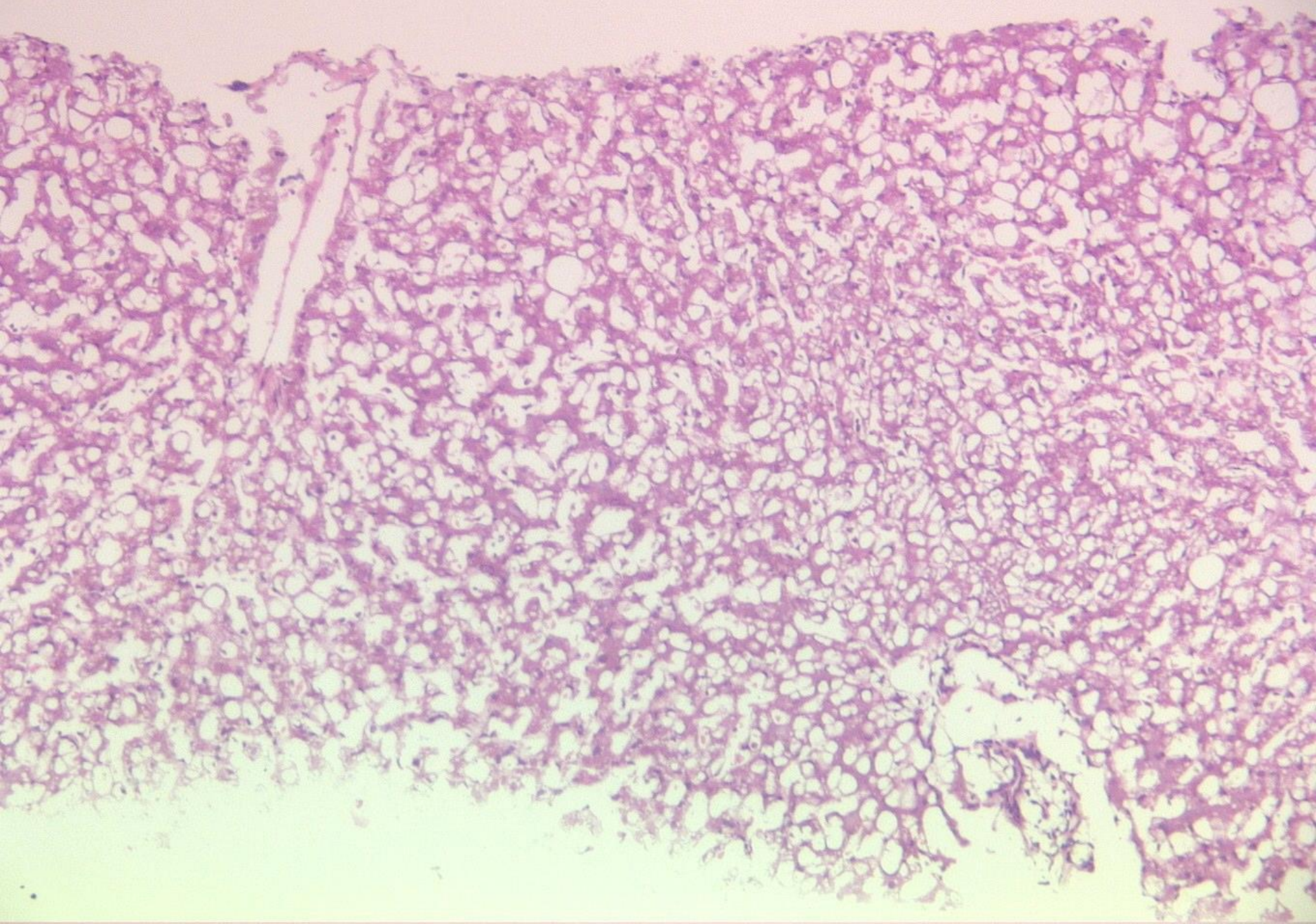
Pathological Features

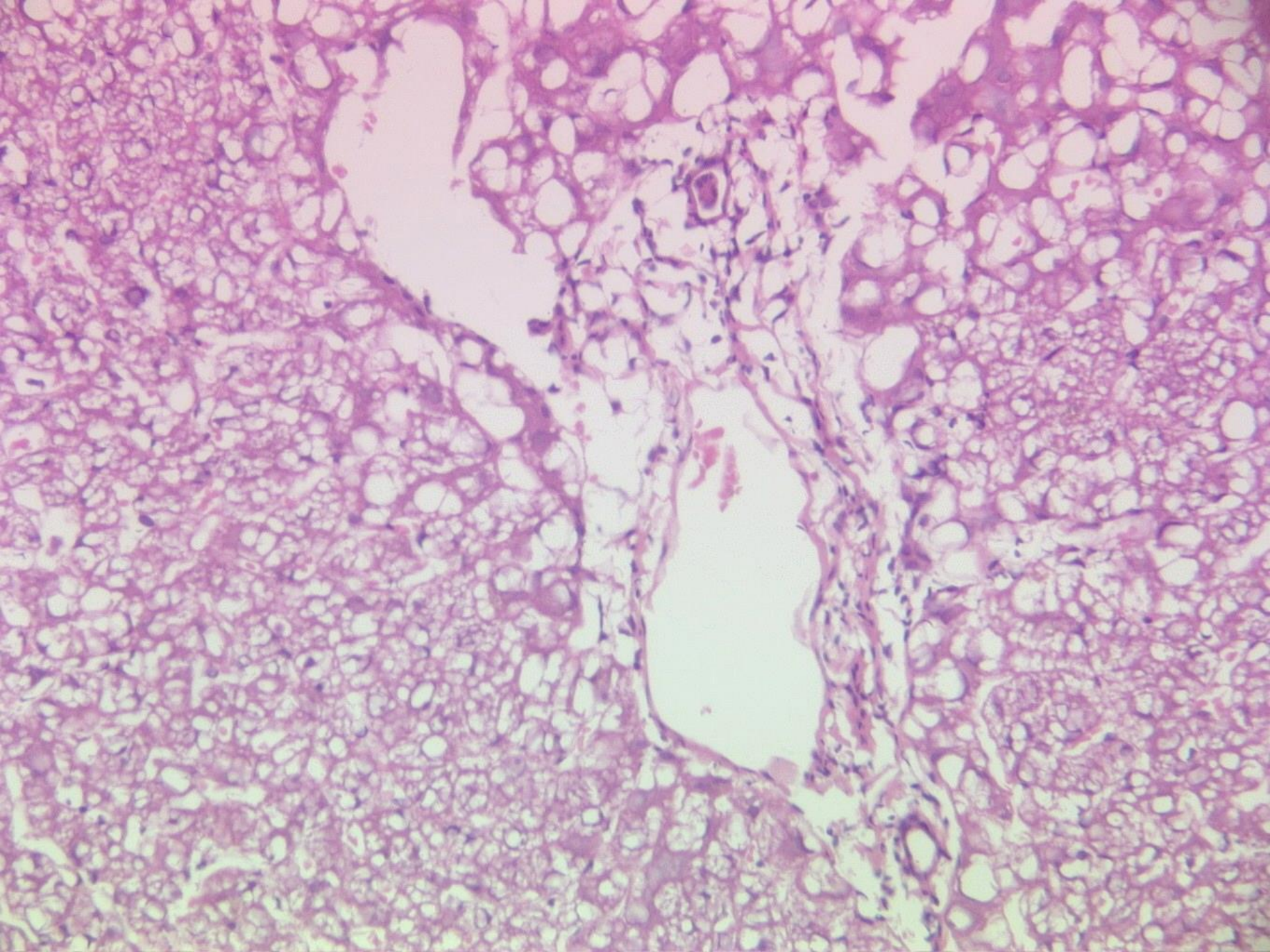
- Most cases associated with diffuse hepatic infiltration (and hepatomegaly)
- may not be detected radiologically
- Occasional cases of T cell lymphoma have extensive hepatic necrosis with only scanty neoplastic lymphoid cells (Blakolmer 2000)

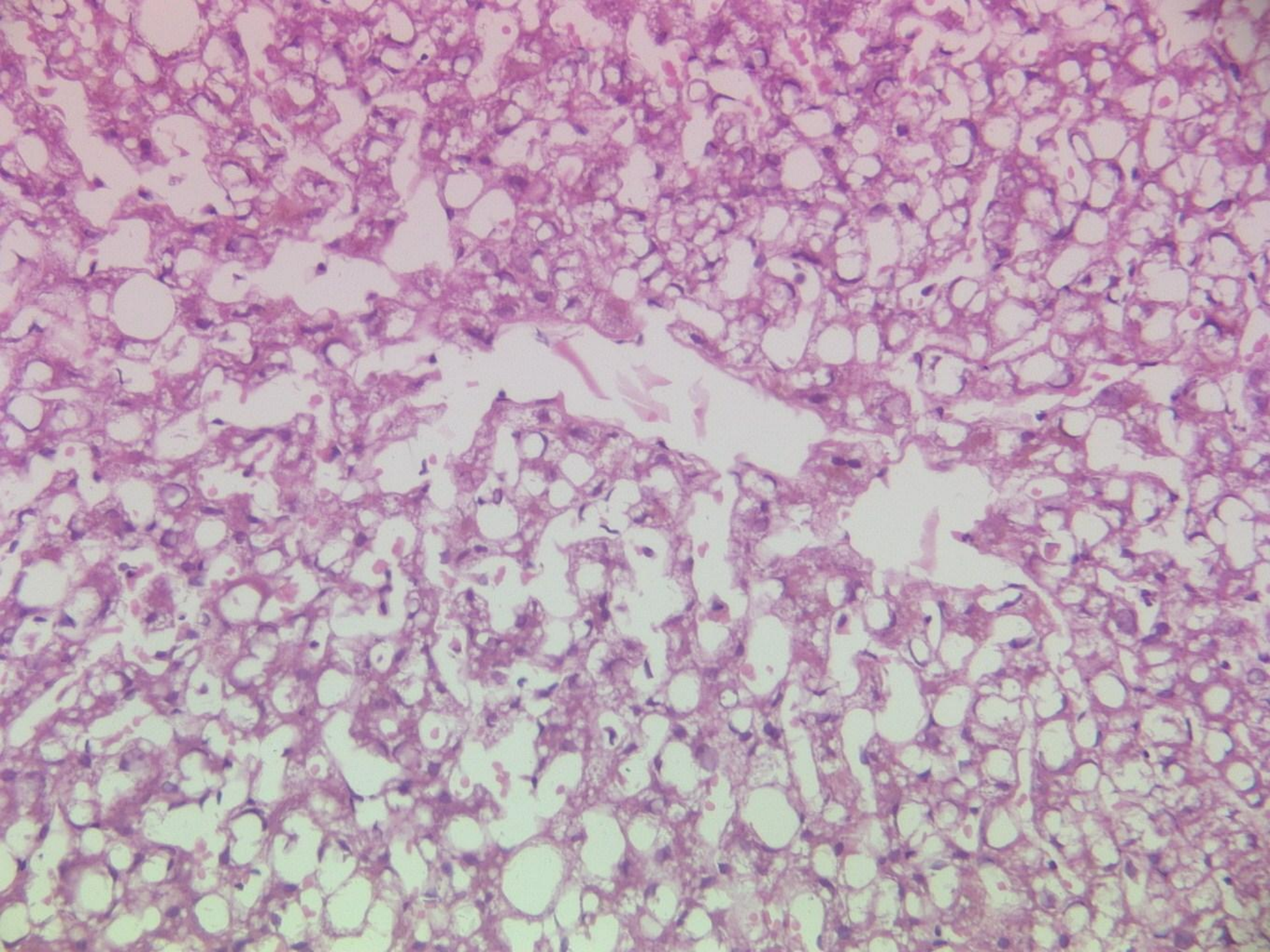
Newcastle C – Dina Tiniakos

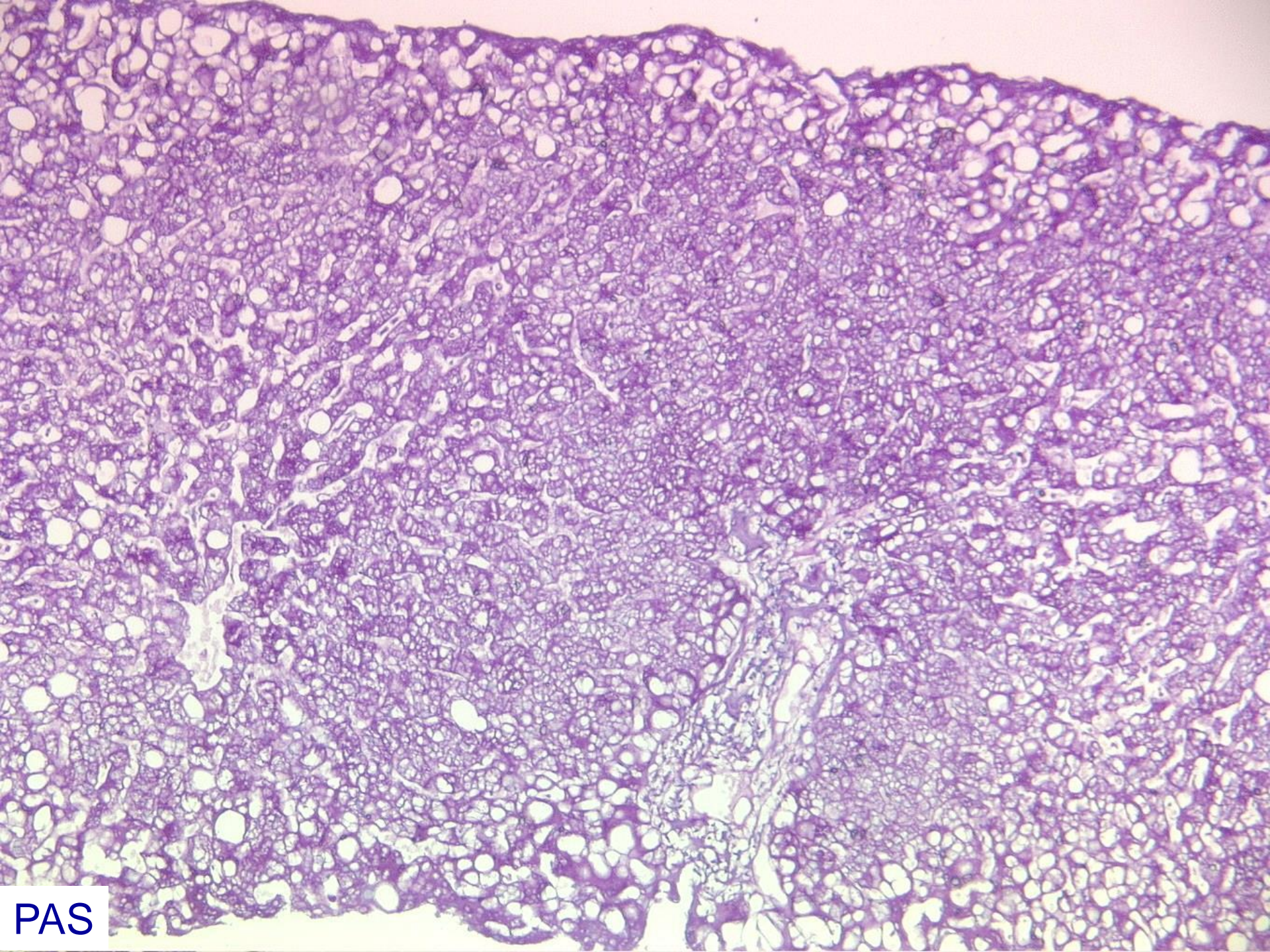
- 46-year-old man
- No significant past medical history
- Shepherd in Northern Greece
(Ioannina, Pindos mountain)
- Cardiac arrest
- Resuscitation for 60 minutes
- Death – organ donation considered
- Frozen section of liver biopsy







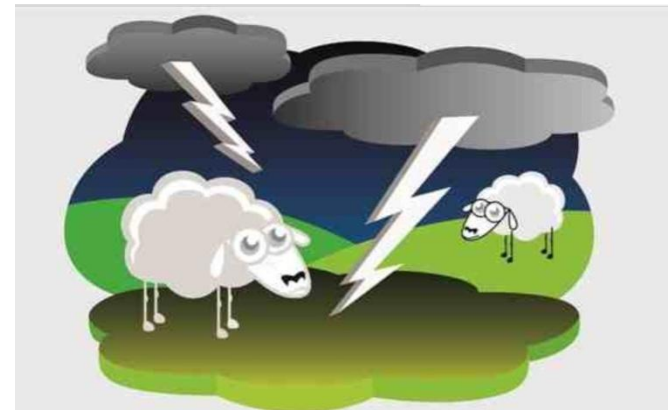




PAS

Summary of histological findings

- extensive tissue injury
- panacinar hepatocyte vacuolation
- no inflammation, ballooning or fibrosis



Newcastle 3:

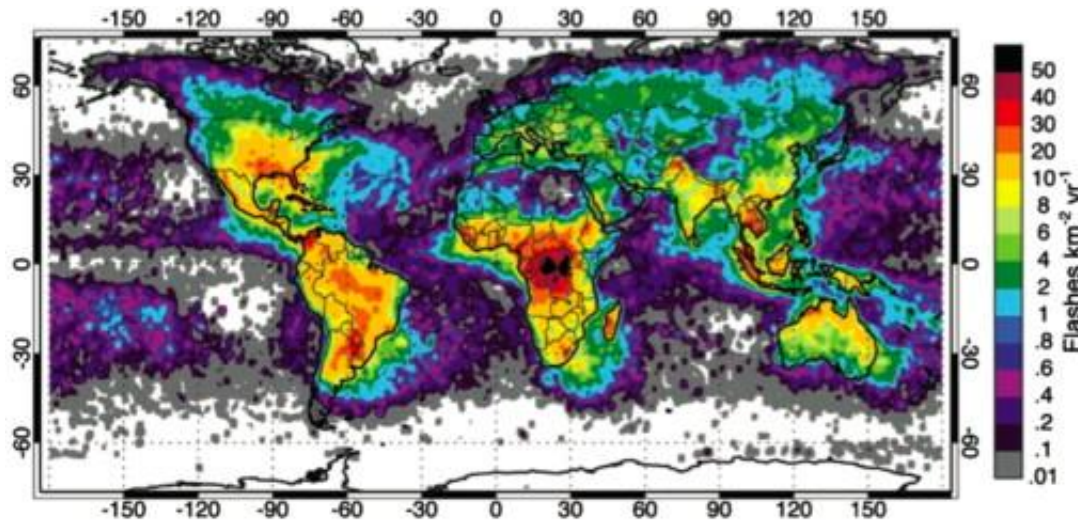
Lightning-related liver injury





Lightning-related injury (keraunopathy)

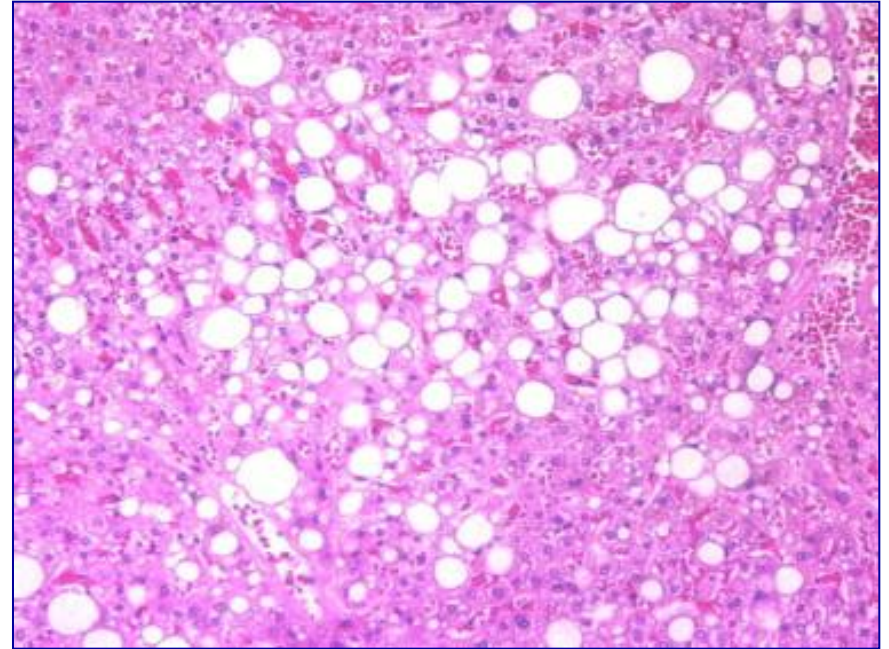
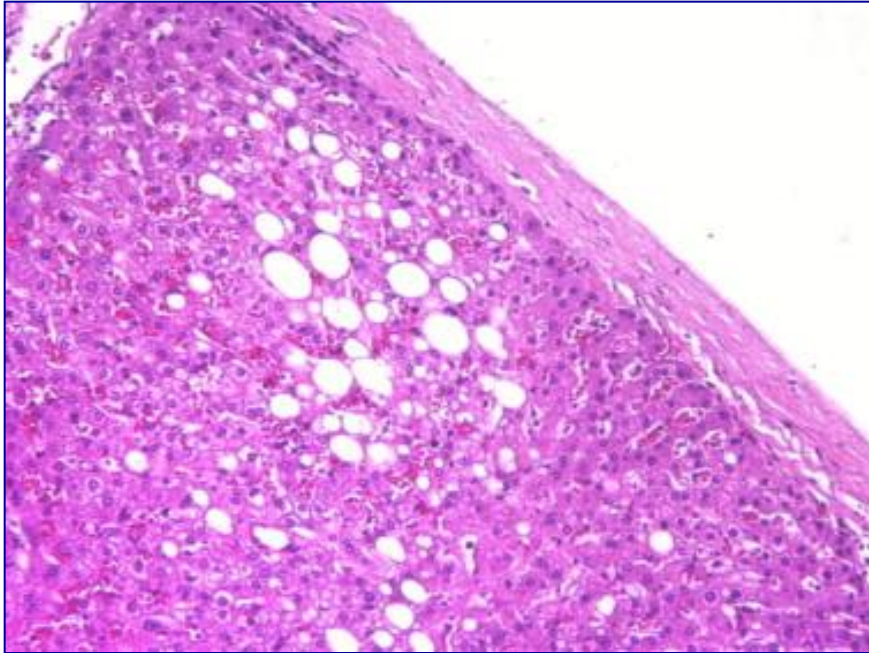
- keraunos in Greek = lightning
- Lightnings strike the earth 100x/sec = 8.000.000x/day
- Risk depends on strike and population density + terrain figures
- 2nd leading cause of weather-related death
- Worldwide mortality 0.2-1.7 deaths/million people



The Lightning Imaging Sensor Global Lightning Distribution Image was obtained from NASA's EOSDIS through the Global Hydrology Resource Center, Huntsville, AL, <http://ghrc.nsstc.nasa.gov/>

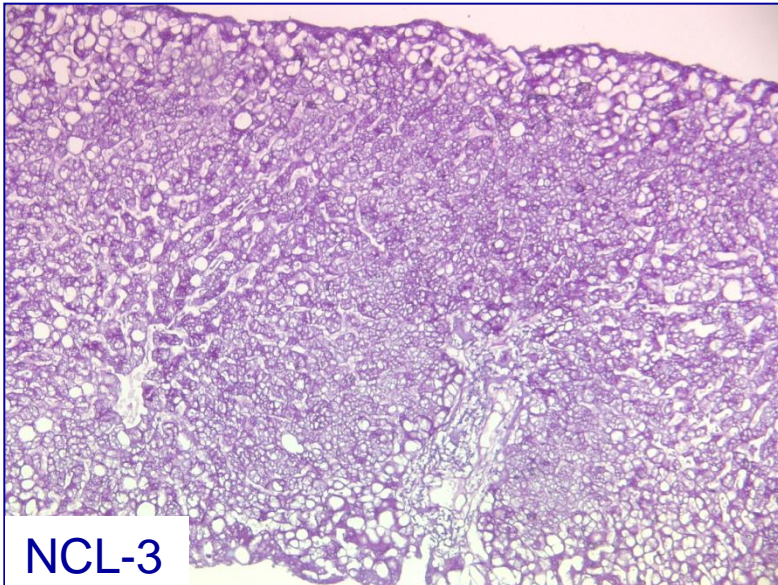


Lightning-related liver injury



One Case Report
Murty, J Forensic Legal Med 2009

- Thermal-type injury
- “Bubbling effect” in the liver



NCL-3

Acute Liver Injury – Circulated Cases

4. OTHER CAUSES (n = 15)

a) Metabolic

- Wilson – Basel B, Groningen A, Paris B, Rochester B, STL B

b) Neoplastic

- T cell lymphoma – Vienna B

c) Vascular

- Congestive/ischemic hepatopathy – Wash A

d) Other/unknown

- Cryptogenic hepatitis in immunosuppressed – Halifax C
- “Seronegative hepatitis” – Bham A, NCL A, Halifax C
- Massive necrosis of unknown aetiology – STL A, NCL B (?)
- Lightning injury – NCL C
- Kawasaki – Wash B

Plans for Next Year.....

Theme for circulated cases

“Patterns of acute liver injury”



And, finally.....

Faculty Dinner - Friday 22nd May 2015

Gnomes meet colleagues from the University and QE Hospital





YFCU EXECUTIVE BOX 29

Executive BOX 28

ALBERTA EXECUTIVE BOX 27

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QuickBooks.

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1.
Denk
(1987)

14.
Tiniakos
(2010)

12.
Wanless
(2004)

8.
Bedossa
(2003)

9.
Goodman
(2003)

7.
Dienes
(2002)

16.
Torbenson
(2011)



HOME

10.
Brunt
(2004)

3.
Burt
(1995)

2.
Callea
(1992)

6.
Terracciano
(1998)

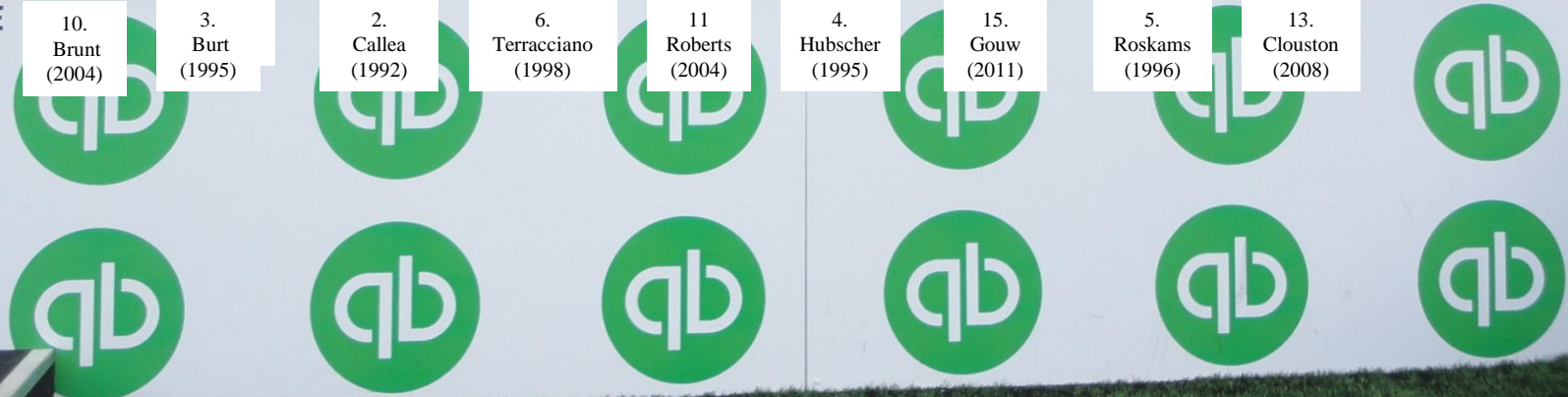
11.
Roberts
(2004)

4.
Hubscher
(1995)

15.
Gouw
(2011)

5.
Roskams
(1996)

13.
Clouston
(2008)





A little later.....

“The Ceremonial Transfer of the Gnomes Hat”



Gnomes 2016: Down under again!

Adelaide, April 27th – 1st May

